DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

# Statistical Review and Evaluation

## CLINICAL STUDIES

| | |
|---|---|
| NDA: | 21-865/N000 |
| Name of drug: | Muraglitazar 2.5 mg, 5 mg Tablets |
| Applicant: | Bristol-Myers Squibb |
| Indication: | Type 2 Diabetes Mellitus |
| Documents reviewed: | \\CDSESUB1\N21865\N_000\2004-12-17 |
| Project manager: | Jena Weber |
| Clinical reviewer: | Robert Misbin, M.D., Julie Golden, M.D. |
| Dates: | Received 12/17/04; user fee (10 months) 10/27/05 |
| Statistical reviewer: | Lee-Ping Pian, Ph.D. |
| Statistics team leader: | Todd Sahlroot, Ph.D. |
| Biometrics division director: | Ed Nevius, Ph.D. |

Keywords: NDA review, clinical studies, analysis of covariance

# 1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

Muraglitazar 2.5 mg and 5 mg were consistently superior to placebo in $HbA_{1c}$ change from baseline for monotherapy or add-on therapies to glyburide or metformin in patients with type 2 diabetes. The phase 2 dose-ranging study showed dose dependent effects in efficacy ($HbA_{1c}$) and safety (CHF, edema, weight gain) comparing muraglitazar 1.5 mg, 5 mg, 10 mg and 20 mg to muraglitazar 0.5 mg. The muraglitazar 1.5 mg dose had efficacy similar to the pioglitazone 15 mg dose as measured by $HbA_{1c}$ change from baseline to week 24 (-0.57%). In naïve patients, the mean $HbA_{1c}$ change was -0.85% for the muraglitazar 1.5 mg group and -0.87% for the pioglitazone 15 mg group (Fig 3, p. 7). Muraglitazar 1.5 mg was statistically significantly better than muraglitazar 0.5 mg in $HbA_{1c}$ change from baseline; however, muraglitazar 2.5 mg was selected as the lowest dose based on dose response modeling. This reviewer recommends that muraglitazar 1.5 mg be considered as an effective dose which was studied only in phase 2 as monotherapy. The mean $HbA_{1c}$ changes were -0.9% to -1.0% for 2.5 mg and were -1.1% to -1.2% for 5 mg dose for all studies from a baseline of approximately 8%. The small incremental efficacy in $HbA_{1c}$ for the 5 mg dose needs to be balanced with the risks of the drug in deciding what should be the highest dose of muraglitazar.

The metformin add-on noninferiority study showed statistical superiority of muraglitazar 5 mg to pioglitazone 30 mg. However, the comparison was not considered dose equivalent since pioglitazone 45 mg is the highest indicated dose and muraglitazar 2.5 mg was similar to pioglitazone 30 mg in $HbA_{1c}$ reduction.

## 1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The submission included one phase 2 and 4 phase 3 studies to support the indication of Pargluva (muraglitazar) 2.5 mg and 5 mg tablets as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus both as monotherapy and in combination with metformin or a sulfonylurea. Table 1 displays the design and number of patients for the 24-week, double-blind studies conducted world wide. Muraglitazar 2.5 mg was not a treatment arm in the phase 2 dose ranging study. The selection of muraglitazar 2.5 mg as the lowest dose in the phase 3 studies was based on projections from dose response modeling.

*Table 1 Phase 2, 3 Clinical Studies in Type 2 Diabetes*

| Study | Design | Centers* (US+PR) | Dose (mg) | # Randomized | Completed (%) |
|---|---|---|---|---|---|
| CV168006 | Monotherapy, Dose ranging, Superiority Mur 1.5, 5, 10, 20 mg vs. Mur 0.5 mg | 293 (176) | Mur 0.5 | 236 | 143 (61%) |
| | | | Mur 1.5 | 259 | 175 (68%) |
| | | | Mur 5 | 245 | 191 (78%) |
| | | | Mur 10 | 249 | 195 (78%) |
| | | | Mur 20 | 239 | 171 (72%) |
| | | | Pio 15 | 251 | 157 (63%) |
| CV168018 | Monotherapy, superiority, vs. placebo | 127 (83) | Mur 2.5 | 111 | 90 (81%) |
| | | | Mur 5 | 114 | 92 (81%) |
| | | | Placebo | 115 | 73 (63%) |
| CV168021 | Combination with glyburide, Superiority, vs. placebo+gly | 218 (132) | Mur 2.5+Gly | 191 | 159 (83%) |
| | | | Mur 5+Gly | 193 | 166 (86%) |
| | | | Placebo+Gly | 199 | 139 (70%) |
| CV168022 | Combination with metformin, Superiority, vs. placebo+met | 251 (144) | Mur 2.5+Met | 233 | 197 (85%) |
| | | | Mur 5+Met | 205 | 179 (87%) |
| | | | Placebo+Met | 214 | 151 (71%) |
| CV168025 | Combination with metformin, Noninferiority, vs. Pioglitazone 30 | 234 (121) | Mur 5+Met | 587 | 522 (89%) |
| | | | Pio 30+Met | 572 | 482 (84%) |
| Total | | | | 4322 | 3343 (77%) |

* US, Puerto Rico and Rest of the world
Mur = muraglitazar; Gly = glyburide; Pio = pioglitazone; Met = metformin

Table 2 displays the sponsor's primary analysis results in $HbA_{1c}$ change from baseline. Muraglitazar 2.5 mg and 5 mg were significantly better than controls in $HbA_{1c}$ change from baseline. The sponsor concluded that "Muraglitazar was clinically effective as monotherapy or as combination therapy with glyburide or metformin, and produced consistent $HbA_{1c}$ lowering at both the 2.5 mg (-0.9% to -1.0%) and 5 mg (-1.1% to -1.2%) doses across all studies. Baseline $HbA_{1c}$ was approximately 8.0% for the randomized treatment groups in all studies."

*Table 2 Sponsor's primary efficacy analysis in $HbA_{1c}$ (%) change from baseline*

| Study | Dose (mg) | n | Baseline | Week 24 | Change (SD) | Mur minus control 2-sided, 95% [C.I.] |
|---|---|---|---|---|---|---|
| CV168006 Dose ranging | Mur 0.5 | 216 | 8.18 (1.06) | 7.92 (1.55) | -0.25 (1.08) | |
| Monotherapy | Mur 1.5 | 235 | 8.15 (1.05) | 7.59 (1.54) | -0.56 (1.13) | -0.31 [-0.52, -0.11] |
| Mur 0.5 controlled | Mur 5 | 227 | 8.23 (1.01) | 7.04 (1.37) | -1.19 (1.12) | -0.92 [-1.13, -0.72] |
| | Mur 10 | 231 | 8.18 (1.05) | 6.66 (1.22) | -1.52 (1.17) | -1.27 [-1.47, -1.06] |
| | Mur 20 | 227 | 8.13 (1.08) | 6.38 (1.18) | -1.75 (1.17) | -1.51 [-1.71, -1.30] |
| | Pio 15 | 230 | 8.31 (1.10) | 7.72 (1.68) | -0.58 (1.18) | -0.31 [-0.52, -0.10] |
| CV168018 | Mur 2.5 | 105 | 8.02 (1.02) | 6.96 (1.02) | -1.06 (1.03) | -0.73 [-0.97, -0.48] |
| Monotherapy | Mur 5 | 110 | 7.89 (0.99) | 6.68 (1.29) | -1.21 (0.99) | -0.91 [-1.15, -0.67] |
| Placebo control | Placebo | 111 | 7.99 (1.05) | 7.67 (1.17) | -0.33 (0.82) | |
| CV168021 | Mur 2.5+Gly | 176 | 7.95 (1.09) | 7.03 (1.00) | -0.93 (1.01) | -1.15 [-1.35, -0.96] |
| Add-on gly | Mur 5+Gly | 189 | 8.17 (1.08) | 6.94 (1.04) | -1.23 (1.01) | -1.37 [-1.55, -1.18] |
| Placebo control | Placebo+Gly | 195 | 8.23 (0.97) | 8.34 (1.26) | 0.11 (1.06) | |
| CV168022 | Mur2.5+Met | 222 | 7.99 (0.99) | 7.08 (1.03) | -0.91 (0.92) | -0.86 [-1.04, -0.67] |
| Add-on met | Mur 5+Met | 198 | 8.00 (0.99) | 6.83 (1.04) | -1.16 (0.99) | -1.11 -1.30, -0.92] |
| Placebo control | Placebo+Met | 197 | 7.97 (1.01) | 7.93 (1.47) | -0.05 (1.12) | |
| CV168025 Add-on met Active control | Mur 5+Met | 569 | 8.12 (0.96) | 6.98 (1.00) | -1.14 (0.90) | -0.29 [-0.39, -0.19] |
| | Pio 30+Met | 550 | 8.13 (1.00) | 7.28 (1.09) | -0.86 (0.97) | |

### 1.3 PRINCIPAL FINDINGS

The 4 phase 3 studies in patients with type 2 diabetes showed consistent efficacy results for muraglitazar 2.5 mg and 5 mg in $HbA_{1c}$ (%) change from baseline to Week 24 or the last post-baseline value prior to Week 24. A total of 6 treatment groups were in the dose ranging study: muraglitazar 0.5, 1.5, 5, 10, 20 mg and pioglitazone 15 mg. The primary efficacy comparison was between each of the muraglitazar doses (1.5, 5, 10, and 20) and the 0.5 mg muraglitazar. All 4 muraglitazar doses were statistically significant better than the 0.5 mg muraglitazar in $HbA_{1c}$ change from baseline. Figure 1 displays differences in the mean $HbA_{1c}$ change from baseline between muraglitazar doses and the control for all 5 studies. Differences from the control for muraglitazar 2.5 mg and 5 mg were -0.73%, and -0.90% for the monotherapy study, and -1.15% and -1.37% for the glyburide add-on study and -0.86% and -1.11% for the metformin add-on study, respectively. Figure 2 displays $HbA_{1c}$ change from baseline over time.

*Figure 1 Mean $HbA_{1c}$ change from baseline difference of muraglitazar to control by treatment group and study*

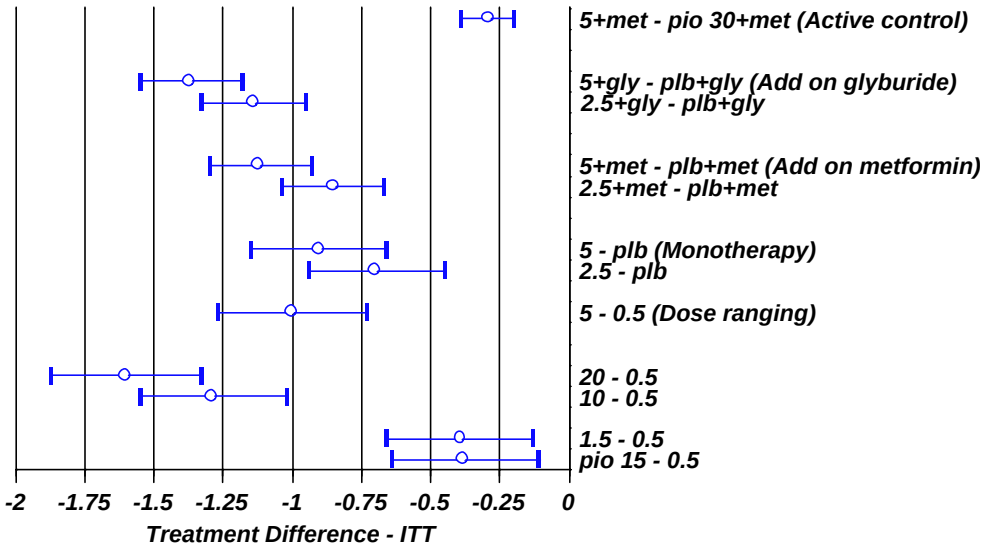
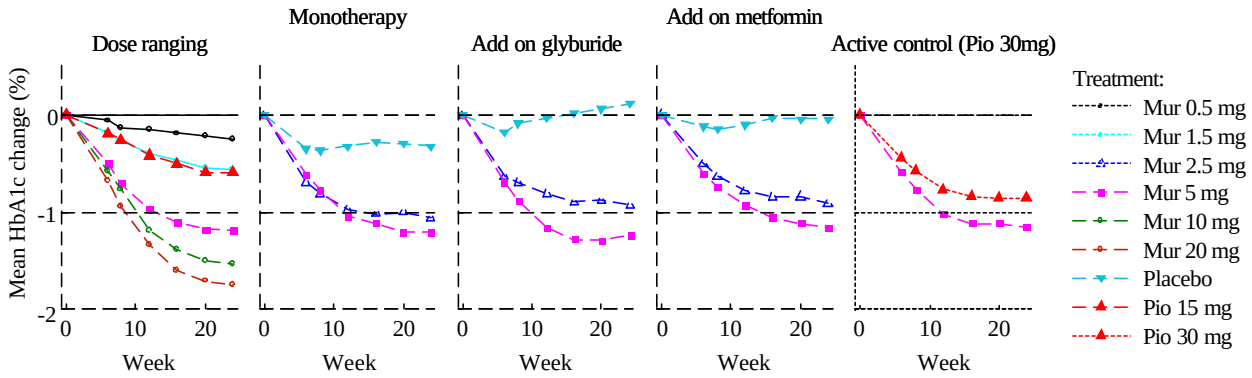


*Figure 2 Mean $HbA_{1c}$ change from baseline over time*




Approximately 2/3 of the patients in the dose ranging monotherapy study and all of the phase 3 monotherapy study were naïve patients. Table 3 displays the least squared means for $HbA_{1c}$ change from baseline stratified by naïve or non naïve patients at randomization for the dose ranging study. Table 4 shows LS means for the phase 3 monotherapy study (all naïve). Figure 3 displays mean $HbA_{1c}$ changes by treatment doses for the naïve and non naïve patients. Baseline $HbA_{1c}$ was approximately 8.0% in the naïve patients. The LSM change from baseline was -0.82% for the muraglitazar 1.5 mg dose and -0.86% for the pioglitazone 15 mg dose in the naïve patients. The LSM changes for the 2.5 mg and 5 mg doses in the monotherapy study were -1.0% and -1.2%, respectively.

*Table 3 Least Squared Mean $HbA_{1c}$ change from baseline by stratum – Dose ranging*

| | | Mur 0.5 mg | | Mur 1.5 mg | | Mur 5 mg | | Mur 10 mg | | Mur 20 mg | | Pio 15 mg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Naïve | n | 146 | | 166 | | 164 | | 168 | | 162 | | 144 | |
| | Baseline Mean (SD) | 8.00 | (1.00) | 8.01 | (0.99) | 8.10 | (1.01) | 8.05 | (1.03) | 8.02 | (1.04) | 8.04 | (1.04) |
| | LSM change from Bsl (SE) | -0.50 | (0.09) | -0.82 | (0.09) | -1.33 | (0.09) | -1.61 | (0.09) | -1.88 | (0.09) | -0.86 | (0.09) |
| Non naïve | n | 77 | | 79 | | 71 | | 72 | | 71 | | 96 | |
| | Baseline Mean (SD) | 8.60 | (1.20) | 8.48 | (1.07) | 8.62 | (1.02) | 8.44 | (1.06) | 8.50 | (1.23) | 8.79 | (1.06) |
| | LSM change from Bsl (SE) | +0.3 | (0.13) | 0.07 | (0.12) | -0.67 | (0.13) | -1.14 | (0.13) | -1.33 | (0.13) | +0.01 | (0.11) |

*Table 4 Mean $HbA_{1c}$ change from baseline – ITT, Monotherapy*

| | Placebo | Mur 2.5 mg | Mur 5 mg |
|---|---|---|---|
| n | 115 | 111 | 114 |
| Baseline Mean (SD) | 8.00(1.04) | 8.05(1.03) | 7.88(0.99) |
| Adjusted Change from Baseline (SE) | -0.32(0.09) | -1.02(0.09) | -1.22(0.09) |

*Figure 3 Mean $HbA_{1c}$ (%) change from baseline by treatment group - Monotherapy*

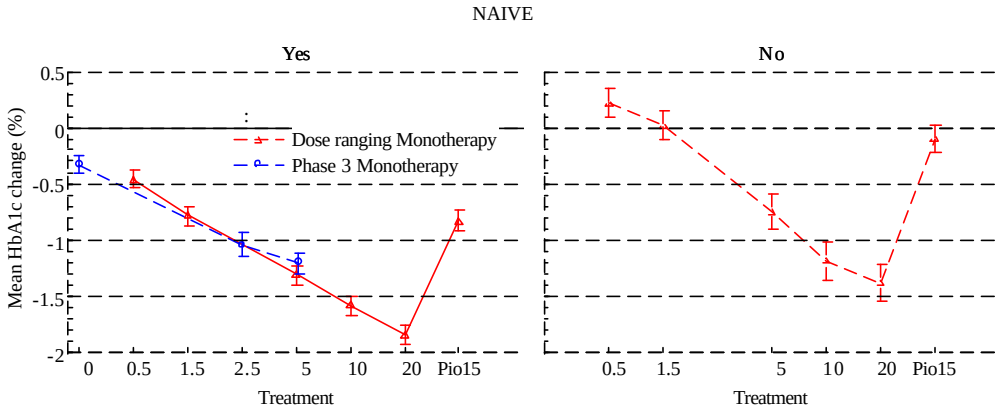
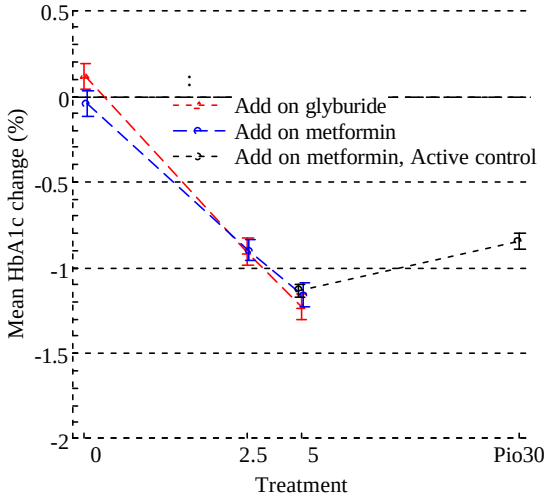



Figure 4 displays the mean $HbA_{1c}$ change by treatment for the 3 add-on studies.

*Figure 4 Mean $HbA_{1c}$ (%) change from baseline by treatment group – Add-on*




**Muraglitazar 1.5/5 mg vs. pioglitazone 15/45 mg**

**A. Dose ranging study Phase B**

None of the studies had a randomized pioglitazone 45 mg treatment group. Patients who lacked glycemic control according to prespecified criteria in the dose ranging study were rescued with titration to a higher study dose in the muraglitazar groups and to pioglitazone 45 mg for patients randomized to pioglitazone 15 mg. Patients in the muraglitazar 20 mg group were discontinued at the time of rescue. This reviewer considers that pioglitazone 15 mg dose was similar to muraglitazar 1.5 mg dose and pioglitazone 30 mg dose was similar to muraglitazar 2.5 mg dose in efficacy (Fig 4).

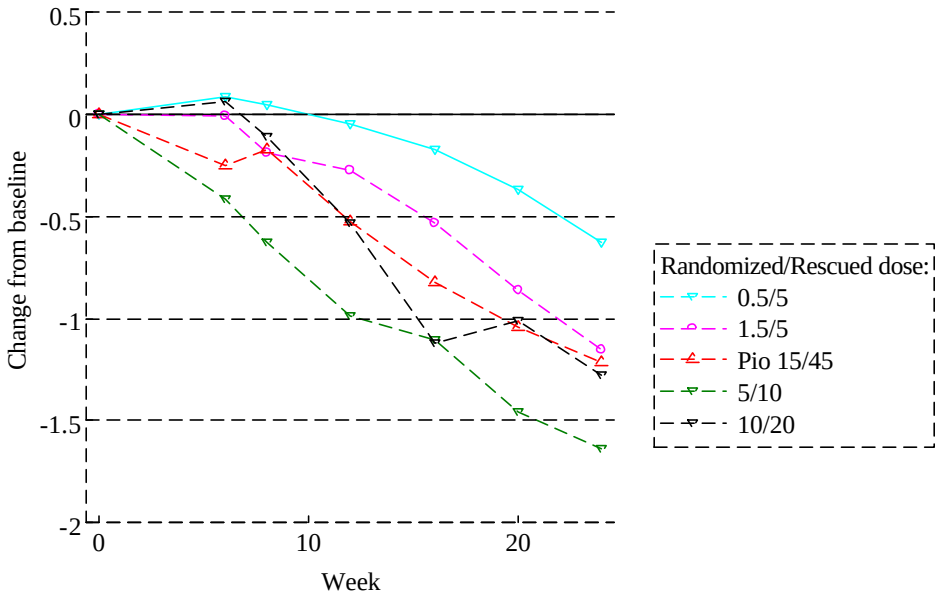
In response to a request from the Division Director, Dr. Orloff, this reviewer compared responses between the muraglitazar 1.5/5 mg and pioglitazone 15/45 mg randomized/rescued treatment groups. The percentages of patients rescued were 14%

(36/259) in the muraglitazar 1.5 mg group and 9% (23/251) in the pioglitazone 15 mg group, respectively. Baseline $HbA_{1c}$ was 8.35% in the muraglitazar 1.5/5 mg patients which was lower than the 8.74% baseline in the pioglitazone 15/45 mg patients. Table 3 displays descriptive statistics at Week 24 for the completers that were not rescued and patients rescued by randomized group and randomized/rescued group, respectively. Figure 5 displays $HbA_{1c}$ change from baseline for the rescued groups over time. Mean $HbA_{1c}$ changes from baseline to Week 24 were similar for patients in the muraglitazar 1.5/5 mg group (-1.15%) and the pioglitazone 15/45 mg group (-1.22%).

*Table 5 Descriptive Statistics for rescued and not rescued patients - completers*

| | | Baseline | | Week 24 | | Change from baseline | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Treatment group | N | Mean | S.D. | Mean | S.D. | Mean | S.D. | Median | Min | Max |
| Mur 0.5 mg | 108 | 7.7 | 0.73 | 6.93 | 0.75 | -0.77 | 0.92 | -0.65 | -3.3 | 2.5 |
| Mur 0.5/5 mg | 34 | 8.06 | 0.77 | 7.43 | 0.87 | -0.62 | 0.96 | -0.7 | -2.3 | 2.2 |
| Mur 1.5 mg | 140 | 7.78 | 0.88 | 6.75 | 0.75 | -1.04 | 0.91 | -1 | -3.9 | 1.2 |
| *Mur 1.5/5 mg* | *36* | *8.35* | *0.76* | *7.2* | *0.82* | *-1.15* | *0.84* | *-1* | *-3.3* | *0.3* |
| Mur 5 mg | 163 | 7.98 | 0.86 | 6.49 | 0.74 | -1.49 | 0.92 | -1.4 | -4.8 | 0.6 |
| Mur 5/10 mg | 25 | 8.88 | 0.86 | 7.25 | 0.78 | -1.64 | 1.11 | -1.7 | -4 | 0.3 |
| Mur 10 mg | 182 | 8.01 | 0.94 | 6.33 | 0.75 | -1.68 | 1 | -1.6 | -4.9 | 1.4 |
| Mur 10/20 mg | 15 | 8.63 | 1.14 | 7.35 | 1.1 | -1.28 | 1.49 | -1.6 | -2.8 | 2.8 |
| Mur 20 mg | 169 | 8.04 | 1.02 | 6.06 | 0.63 | -1.97 | 0.99 | -1.8 | -5.2 | -0.1 |
| Pio 15 mg | 126 | 7.83 | 0.89 | 6.75 | 0.76 | -1.08 | 0.81 | -1 | -3.8 | 0.9 |
| *Pio 15/45 mg* | *23* | *8.74* | *1* | *7.53* | *0.83* | *-1.22* | *1.02* | *-1.3* | *-3.1* | *0.5* |

*Figure 5 Mean $HbA_{1c}$ change from baseline over time – Rescued completers*




Muraglitazar 1.5/5 mg vs. pioglitazone 15/45 – Dose ranging, Phase C

At year 2 interim, the mean changes and standard deviations from baseline for 20 short term rescued patients in muraglitazar 1.5/5 mg (max muraglitazar 5 mg) and 23 short term rescued patients in pioglitazone 15/45 (max pioglitazone 45 mg) were -1.76% (1.00) and -1.69% (1.38), respectively.

Figure 6 displays the mean $HbA_{1c}$ changes from baseline by time for patients completed 104 weeks of randomized treatment (BMS 1.5, 5, 10, 20, or PIO 15). Patients in the BMS 1.5/5 group or PIO 15/45 group were either rescued in the short term phase or titrated once in the long term phase to their maximum doses. The mean (SD) $HbA_{1c}$ change from baseline was -1.25% (1.16) for the 40 patients in the muraglitazar 1.5/5 mg group and was -1.05% (1.26) for the 34 patients in the pioglitazone 15/45 mg group. The baseline $HbA_{1c}$ mean was 8.0% (0.9%) for both groups.

Figure 7 displays the mean $HbA_{1c}$ change from baseline by time for the "ITT" patients with LOCF data. The mean (SD) $HbA_{1c}$ changes from baseline were -0.43% (1.44) for the 97 patients in muraglitazar 1.5/5 group and -0.37% (1.45) for the 138 patients in the pioglitazone 15/45 group. The $HbA_{1c}$ baseline means were 8.54% and 8.74%, respectively.

*Figure 6 Mean $HbA_{1c}$ change from baseline by time - completers*

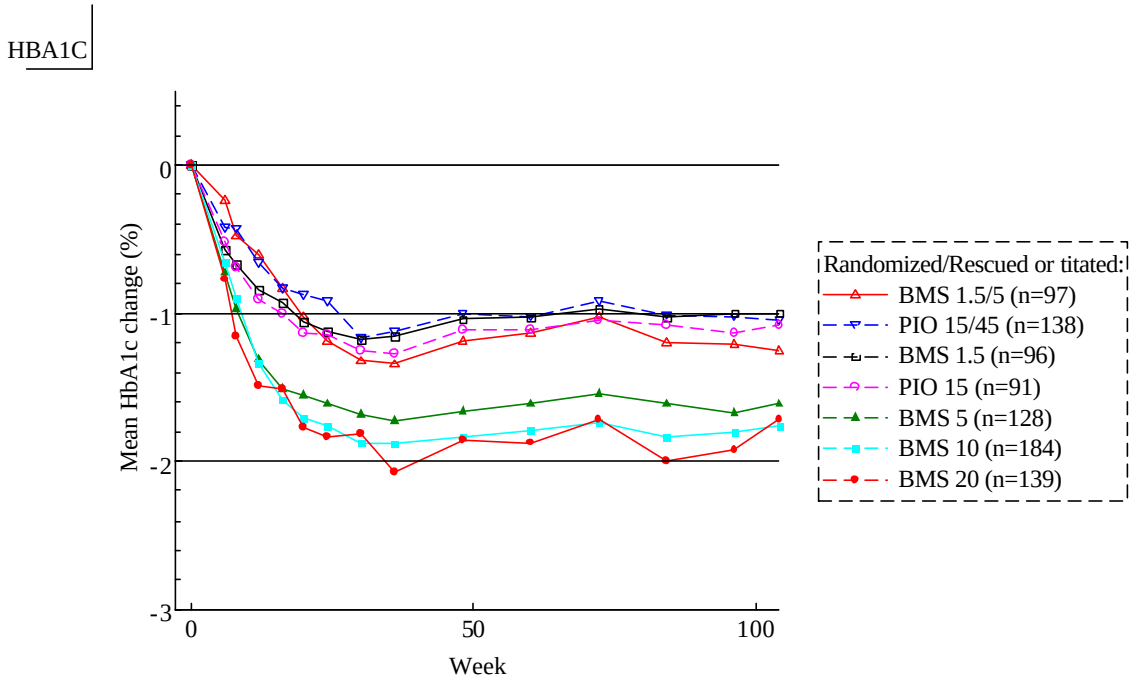
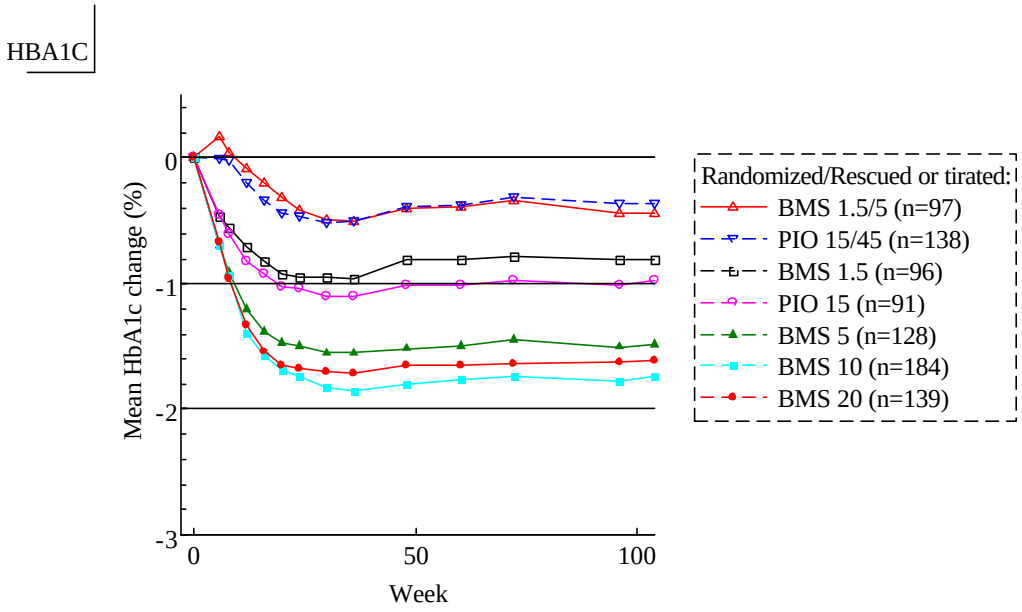


*Figure 7 Mean $HbA_{1c}$ by time ( LOCF)*




## Safety

Compared to placebo, weight changes from baseline were approximately 2 kg in muraglitazar 2.5 mg-treated patients and 3 kg for monotherapy and 3.5 kg for add-on therapies for the muraglitazar 5.0 mg treated patients. Figure 8 displays the weight change over time and Figure 9 the mean differences between muraglitazar treatment groups and the control group in weight change from baseline with the 2-sided, 95% confidence intervals.

*Figure 8 Mean weight change from baseline over time*

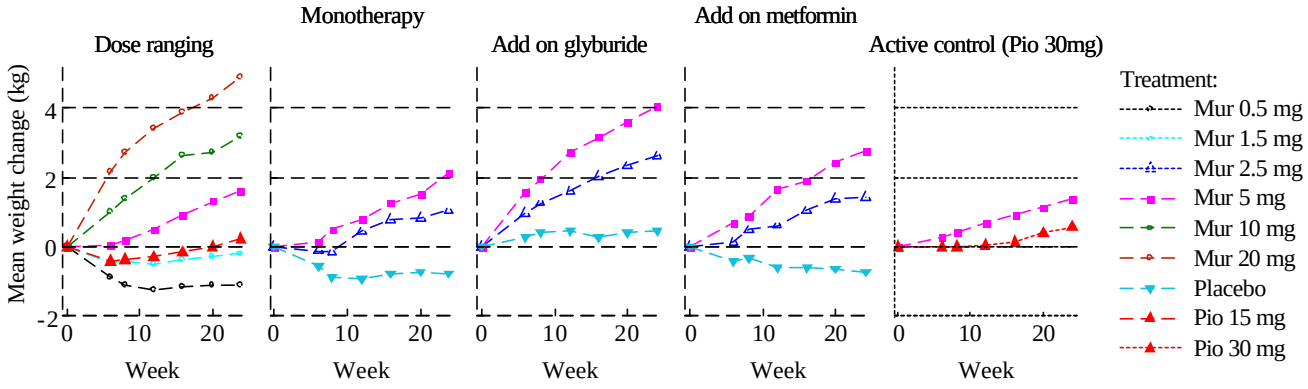


*Figure 9 Difference from control in weight change from baseline*

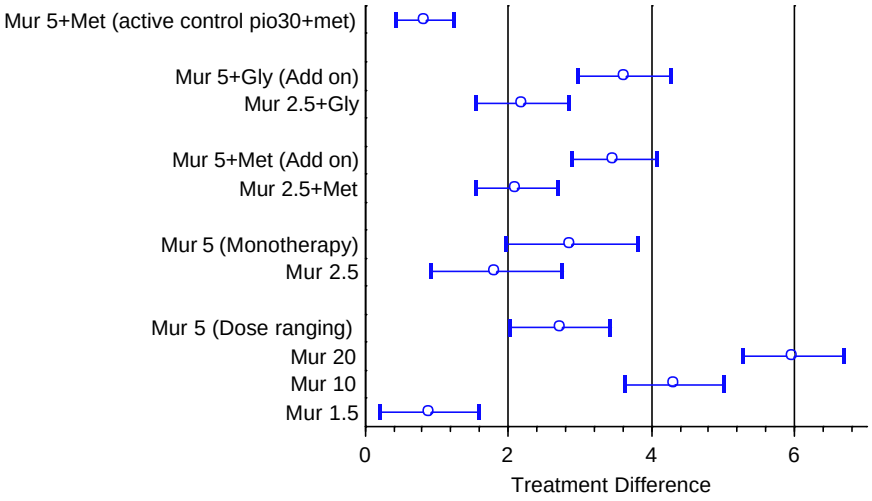


Table 6 summarizes AE discontinuation and the cardiac disorder subset (i.e., discontinuations specifically due to cardiac disorder) during the 24 week treatment phase. The Cochran-Armitage trend test for the AE discontinuation was statistically significant ($p<0.01$) for the dose ranging study. There were no cardiac discontinuations in the placebo-treated patients or in the monotherapy muraglitazar-treated patients during double blind treatment. The analysis of the 2 add-on studies stratified by type of background therapy (glyburide or metformin) was statistically significant using the Cochran-Armitage trend test.

*Table 6 AE discontinuation and Cardiac AE discontinuation*

| Study | Dose (mg) | n | AE # (%) | Cardiac |
|---|---|---|---|---|
| CV168006 Dose ranging Monotherapy | Mur 0.5 | 236 | 6 (2.5%) | 0 |
| Mur 0.5 controlled | Mur 1.5 | 259 | 11 (4.2%) | 1 (0.4%) |
| | Mur 5 | 245 | 10 (4.1%) | 0 |
| | Mur 10 | 249 | 21 (8.4%) | 3 (1.2%) |
| | Mur 20 | 237 | 31 (13.1%) | 2 (0.8%) |
| P value | | | P<0.01 | P=0.08 |
| | Pio 15 | 251 | 12 (4.8%) | 1 (0.4%) |
| CV168018 Monotherapy Placebo control | Placebo | 115 | 3 (2.6%) | 0 |
| | Mur 2.5 | 111 | 3 (2.7%) | 0 |
| | Mur 5 | 114 | 4 (3.5%) | 0 |
| P value | | | P=0.70 | na |
| CV168021 Add-on gly Placebo control | Placebo+Gly | 199 | 5 (2.5%) | 0 |
| | Mur 2.5+Gly | 191 | 6 (3.1%) | 2 (1.0) |
| | Mur 5+Gly | 193 | 10 (5.2%) | 3 (1.6) |
| P value | | | P=0.18 | P=0.11 |
| CV168022 Add-on met Placebo control | Placebo+Met | 214 | 3 (1.4%) | 0 |
| | Mur2.5+Met | 233 | 7 (3.0%) | 2 (0.9%) |
| | Mur 5+Met | 205 | 10 (4.9%) | 2 (1.0%) |
| 2-sided 95% p value | | | P=0.05 | P=0.23 |
| 2 Add-on studies stratified p value | | | P=0.02 | P=0.04 |
| CV168025 Add-on met Active control | Mur 5+Met | 587 | 16 (2.7%) | 2 (0.3%) |
| | Pio 30+Met | 572 | 9 (1.6%) | 2 (0.3%) |
| | | | P=0.23 | P=1.00 |
| 3 Add-on studies stratified p value | | | P=0.006 | P=0.085 |

Mur = muraglitazar; Gly = glyburide; Pio = pioglitazone; Met = metformin

## Death and Cardiovascular Death

Patients in the monotherapy studies were to be 'naïve' to antidiabetic drug, hence dissimilar in disease progression to patients in the combination studies who were inadequately controlled with sulfonylurea or metformin. The phase 3 monotherapy study had no extension period and no deaths. The combination studies were all phase 3 studies with an ongoing extension phase. Table 7 displays the analysis of total deaths and a subset of total deaths, namely, cardiovascular death by study. The analysis was stratified by the combination study. Both analyses yielded nominally significant results (p=0.01). For the pooled analysis, the odds-ratios of muraglitazar 2.5 mg and 5.0 mg over placebo for CV death were 4.5 and 19.8, respectively.

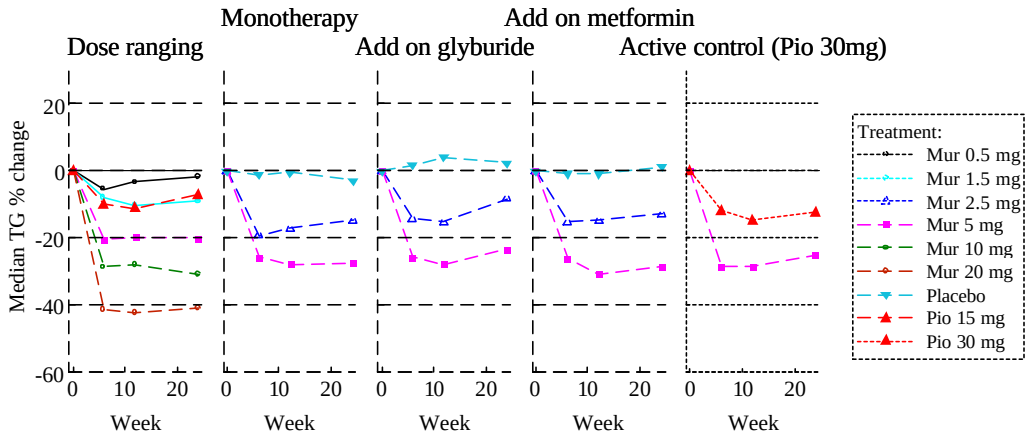
*Table 7 Death and CV death*

| Study | Dose (mg) | n | Death # | CV death |
|---|---|---|---|---|
| CV168006 Dose ranging Monotherapy | Mur 0.5 | 236 | 0 (0.00%) | 0 (0.00%) |
| Mur 0.5 controlled | Mur 1.5 | 259 | 2 (0.77%) | 0 (0.00%) |
| | Mur 5 | 245 | 1 (0.41%) | 0 (0.00%) |
| | Mur 10 | 249 | 1 (0.40%) | 0 (0.00%) |
| | Mur 20 | 237 | 1 (0.42%) | 1 (0.42%) |
| P value | | | P=0.76 | P=0.19 |
| | Pio 15 | 251 | 1 (0.40%) | 0 (0.00%) |
| CV168018 Monotherapy Placebo control | Placebo | 115 | 0 (0.00%) | 0 (0.00%) |
| | Mur 2.5 | 111 | 0 (0.00%) | 0 (0.00%) |
| | Mur 5 | 114 | 0 (0.00%) | 0 (0.00%) |
| P value | | | NA | NA |
| CV168021 Add-on Gly, Placebo control | Placebo+Gly | 199 | 1 (0.50%) | 0 (0.00%) |
| | Mur 2.5+Gly | 191 | 0 (0.00%) | 0 (0.00%) |
| | Mur 5+Gly | 193 | 2 (1.04%) | 1 (0.52%) |
| P value | | | P=0.52 | P=0.33 |
| CV168022 Add-on Met, Placebo control | Placebo+Met | 214 | 0 (0.00%) | 0 (0.00%) |
| | Mur2.5+Met | 233 | 2 (0.86%) | 1 (0.43%) |
| | Mur 5+Met | 205 | 3 (1.46%) | 1 (0.49%) |
| 2-sided 95% p value | | | P=0.10 | P=0.43 |
| stratified p value (2 add-on studies) | | | P=0.08 | P=0.18 |
| CV168025 Add-on Met Active control | Pio 30+Met | 572 | 1 (0.17%) | 0 (0.00%) |
| | Mur 5+Met | 587 | 6 (1.02%) | 5 (0.85%) |
| p-value | | | P=0.12 | P=0.03 |
| stratified p-value (3 add-on studies) | | | P=0.01 | P=0.01 |
| Pooled p-value (3 Add-on studies) | Placebo | 413 | 1 (0.24%) | 0 (0.00%) |
| | Mur 2.5 | 424 | 2 (0.47%) | 1 (0.24%) |
| | Mur 5.0 | 985 | 11 (1.12%) | 7 (0.71%) |
| Pooled trend test p-value | | | P=0.07 | P=0.06 |
| Total Death | | | 21 | 9 |

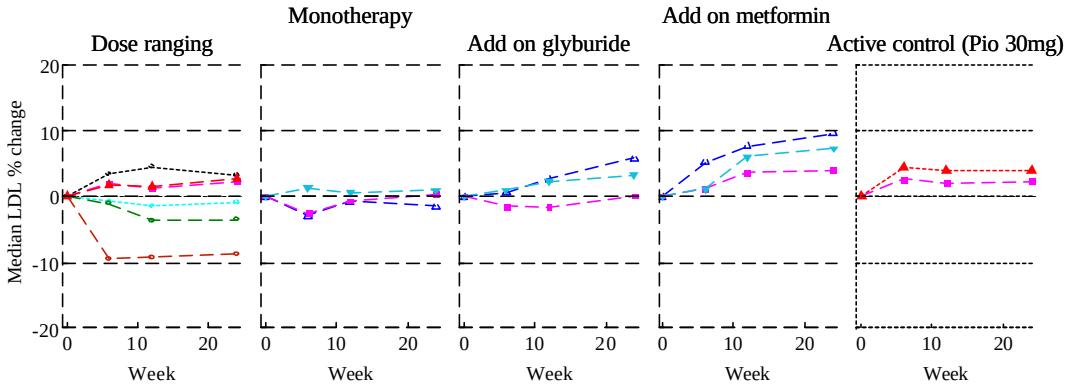
Mur = muraglitazar; Gly = glyburide; Pio = pioglitazone; Met = metformin

The graphic displays show the lipid profiles and secondary outcome variables with the legend following the triglyceride graph. The primary endpoint for lipid outcomes was week 12 prior to which no change of lipid medication was allowed.

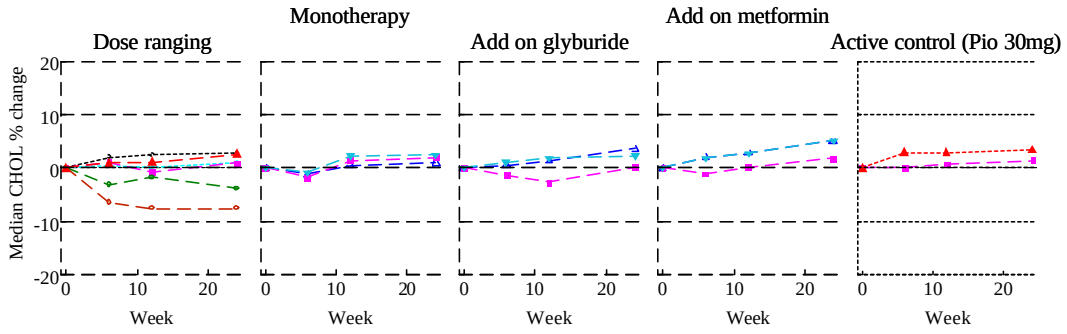
TRIGF



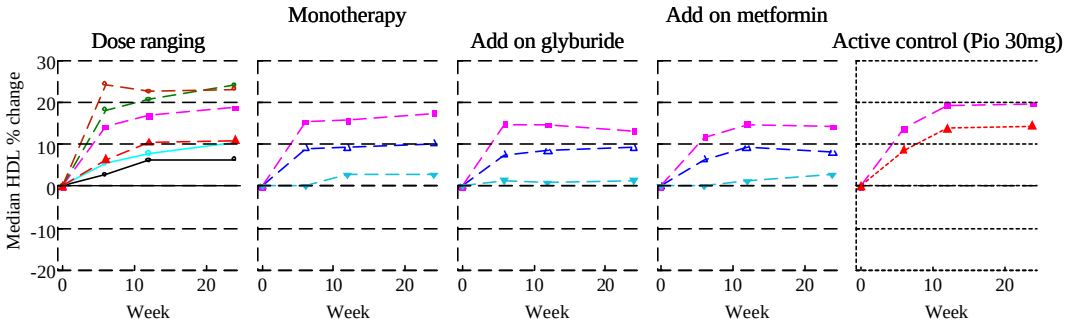

LDLC



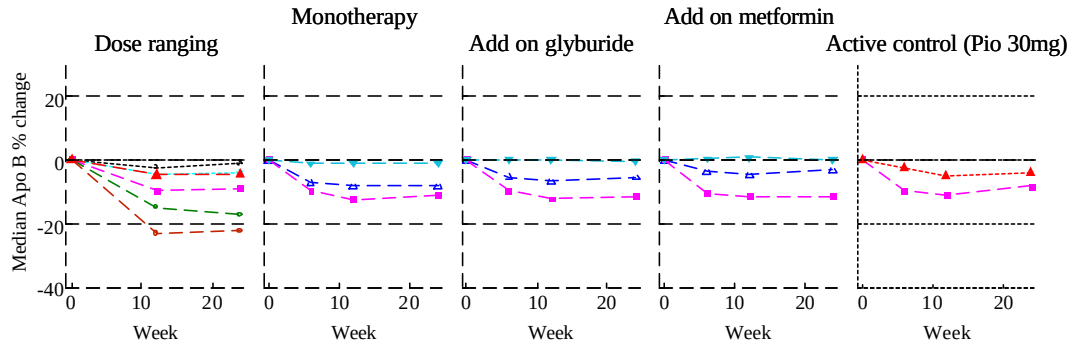

CHOL



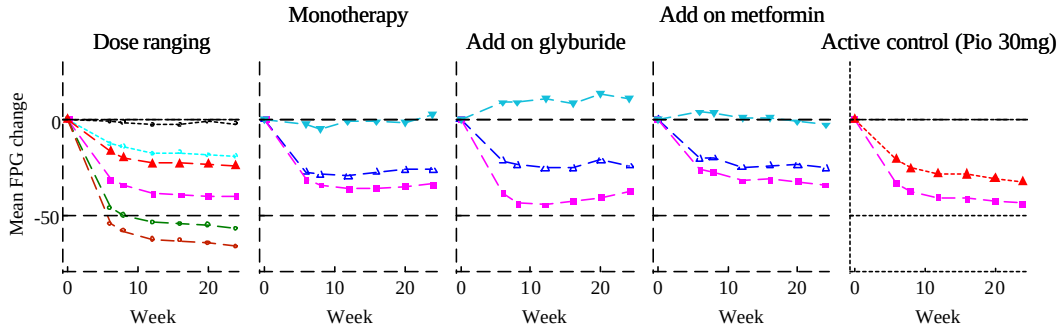
HDLC



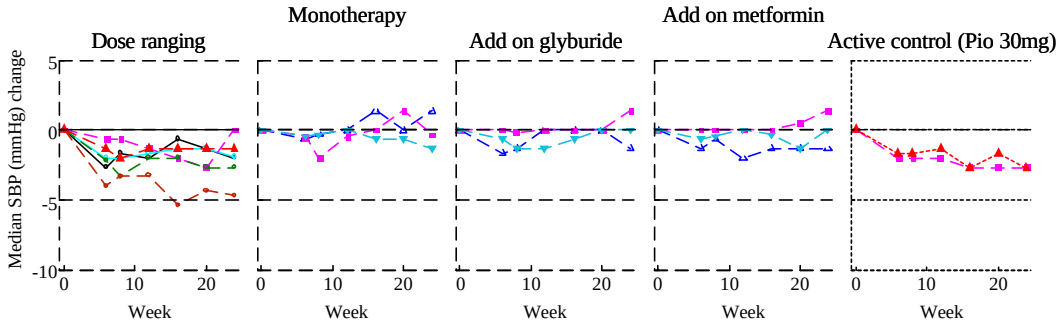

APOB



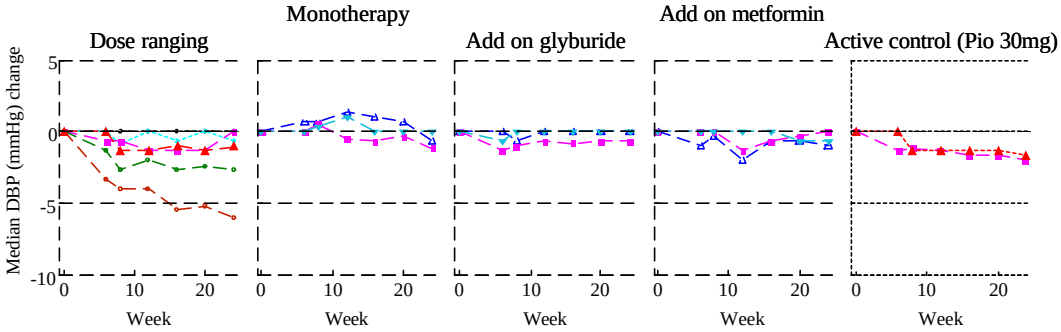

PGLUF



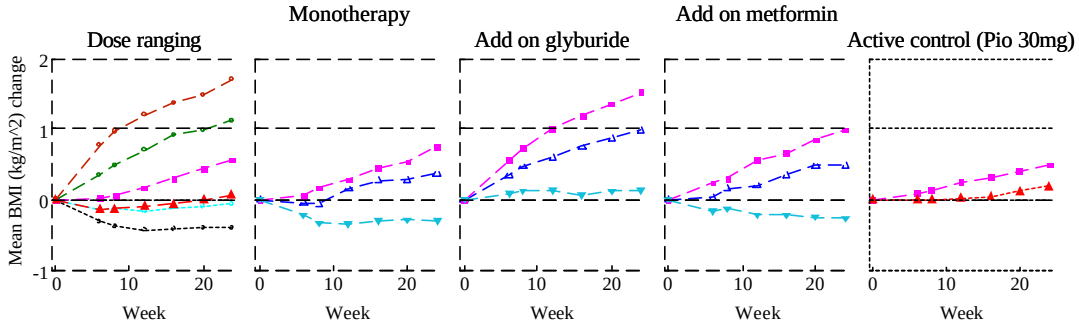
BPSYS



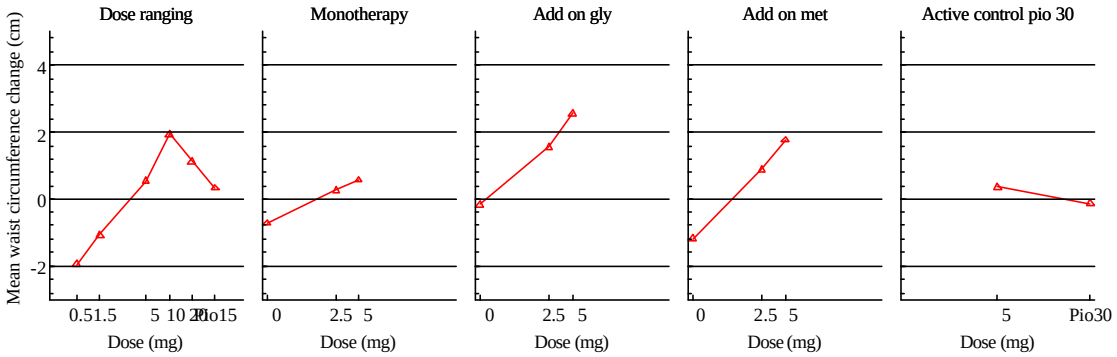

BPDIA




BMI



Waist Circumference




## 2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 2.1 INTRODUCTION AND BACKGROUND

The submission included five, 24-week studies to support the indication of muraglitazar in patients with type 2 diabetes. Study CV168006 was a phase 2 monotherapy dose-ranging study that compared muraglitazar 1.5, 5, 10, and 20 mg with muraglitazar 0.5 mg. Based on dose-response modeling and the rate of $HbA_{1c}$<7.0% in the muraglitazar 1.5 mg group being 40%, the 2.5 mg dose was selected as the lower dose for Phase 3 studies. The phase 3 monotherapy study CV168018 compared muraglitazar 2.5 mg or 5 mg to placebo. Studies CV168021 and CV168022 compared muraglitazar 2.5 mg or 5 mg in combination with glyburide or metformin to placebo in combination with glyburide or metformin. The noninferiority study CV168025 compared muraglitazar 5 mg in combination with metformin to pioglitazone 30 mg in combination with metformin.

### 2.2 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

#### 2.2.1 SPONSOR'S RESULTS AND CONCLUSIONS

The primary efficacy variable for the studies was $HbA_{1c}$ change from baseline to week 24 or the last post baseline follow up after 6 weeks of treatment prior to week 24. The analysis of covariance (ANCOVA) model included randomization group as the fixed effect and the baseline $HbA_{1c}$ as a covariate. A sequential testing procedure was applied to adjust for multiple comparisons in the superiority studies. The margin was 0.25% for the noninferiority study.

##### *2.2.1.1 Dose Ranging Study - CV168006*

Patients discontinued prematurely were included in the analysis of glycemic parameters (fasting insulin, fasting plasma glucose, fructosamine) only if they received at least 8 days of treatment (6 weeks for $HbA_{1c}$). A sensitivity analysis on change from baseline in $HbA_{1c}$ was carried out including patients who either dropped out or went on rescue therapy prior to receiving at least 6 weeks of treatment.

A total of 1477 patients were randomized, 1226 to muraglitazar and 251 to pioglitazone 15 mg. Only muraglitazar-treated patients were included in the primary efficacy analysis. Of the 1226 muraglitazar-treated patients, 1136 (92.7%) were included in the primary analysis. For patients discontinued with rescue medication, the last observation prior to rescue was carried forward. There was a dose response in $HbA_{1c}$ mean change from baseline for the muraglitazar doses (Table 8).

*Table 8 Sponsor's primary analysis of the $HbA_{1c}$ change from baseline – Dose ranging monotherapy*

| | Mur 0.5 mg N=236 | Mur 1.5 mg N=259 | Mur 5 mg N=245 | Mur 10 mg N=249 | Mur 20 mg N=237 |
|---|---|---|---|---|---|
| n | 216 | 235 | 227 | 231 | 227 |
| Baseline Mean (SD) | 8.18 (1.06) | 8.15 (1.05) | 8.23 (1.01) | 8.18 (1.05) | 8.13 (1.08) |
| Week 24 LOCF Mean (SD) | 7.92 (1.55) | 7.59 (1.54) | 7.04 (1.37) | 6.66 (1.22) | 6.38 (1.18) |
| Mean Change from Bsl. (SD) | -0.25 (1.08) | -0.56 (1.13) | -1.19 (1.12) | -1.52 (1.17) | -1.75 (1.17) |
| ANCOVA Adjusted Mean (SE) | -0.25 ( 0.08) | -0.57 ( 0.07) | -1.18 ( 0.07) | -1.52 ( 0.07) | -1.76 ( 0.07) |
| Difference vs Mur 0.5 mg | | -0.31 (0.10) | -0.92 (0.11) | -1.27 (0.11) | -1.51 (0.11) |
| 95% two-sided CI | | [ -0.40, -0.11] | [ -0.71, -0.42] | [ -1.32, -1.03] | [ -1.66, -1.38] |

### *2.2.1.2 Monotherapy Study - CV168018*

A total of 340 patients were randomized, 111 to the muraglitazar 2.5 mg group, 114 to the muraglitazar 5 mg group and 115 to the placebo group. Of the 340 patients, 326 (95.9%) received at least 6 weeks of treatment were in the primary efficacy analysis. The mean difference and 2-sided 95% confidence intervals between the 2.5 mg, 5 mg and placebo were -0.73% [-0.97, -0.48] and -0.91% [-1.15, -0.67], respectively (Table 9).

*Table 9 Sponsor's analysis in $HbA_{1c}$ change from baseline - Monotherapy*

| | Mur 2.5 mg N=111 | Mur 5.0 mg N=114 | Placebo N=115 |
|---|---|---|---|
| n | 105 | 110 | 111 |
| Baseline Mean (SD) | 8.02 (1.02) | 7.89 (0.99) | 7.99 (1.05) |
| Week 24 LOCF Mean (SD) | 6.96 (1.02) | 6.68 (1.29) | 7.67 (1.17) |
| Mean Change from Bsl. (SD) | -1.06 (1.03) | -1.21 (0.99) | -0.33 (0.82) |
| ANCOVA Adjusted Mean (SE) | -1.05 (0.09) | -1.23 (0.09) | -0.32 (0.09) |
| Difference vs. PLA | -0.73 (0.12) | -0.91 (0.12) | |
| 95% two-sided CI | [-0.97, -0.48] | [-1.15, -0.67] | |

### *2.2.1.3 Combination with glyburide - CV168021*

A total of 583 patients were randomized, 191 to muraglitazar 2.5 mg+glyburide, 193 to muraglitazar 5.0 mg+glyburide, and 199 to placebo+glyburide. Of those 560 (96.1%) patients were in the primary efficacy analysis. The mean difference and 2-sided 95% confidence intervals between the 2 muraglitazar+glyburide groups and placebo+glyburide group were -1.15 [ -1.35, -0.96] (2.5 mg) and -1.37 [ -1.55, -1.18] (5 mg) (Table 10).

*Table 10 Sponsor's analysis in $HbA_{1c}$ change from baseline - Combination with glyburide*

| | MUR 2.5+GLY N=191 | MUR 5+GLY N=193 | PLA+GLY N=199 |
|---|---|---|---|
| n | 176 | 189 | 195 |
| Baseline Mean (SD) | 7.95 (1.09) | 8.17 (1.08) | 8.23 (0.97) |
| Week 24 LOCF Mean (SD) | 7.03 (1.00) | 6.94 (1.04) | 8.34 (1.26) |
| Mean Change from Bsl. (SD) | -0.93 (1.01) | -1.23 (1.01) | 0.11 (1.06) |
| ANCOVA Adjusted Mean (SE) | -1.00 (0.07) | -1.21 (0.07) | 0.16 (0.07) |
| Difference vs. PLA+GLY | -1.15 (0.10) | -1.37 (0.10) | |
| 95% two-sided CI | [ -1.35, -0.96] | [ -1.55, -1.18] | |

*2.2.1.4 Combination with metformin - CV168022*

A total of 652 patients were randomized, 233 to muraglitazar 2.5 mg+metformin, 205 to muraglitazar 5.0 mg+metformin and 214 to placebo+metformin. Of those 617 (94.6%) patients were in the primary efficacy analysis. The mean differences and the 2-sided 95% confidence intervals between the 2.5 mg and 5 mg muraglitazar+metformin groups and placebo+metformin group were -0.86 [-1.04, -0.67] and -1.11 [-1.30, -0.92], respectively (Table 11).

*Table 11 Sponsor's analysis in $HbA_{1c}$ change from baseline - Combination with metformin*

| | MUR 2.5+MET N=233 | MUR 5+MET N=205 | PLA+MET N=214 |
|---|---|---|---|
| n | 222 | 198 | 197 |
| Baseline Mean (SD) | 7.99 (0.99) | 8.00 (0.99) | 7.97 (1.01) |
| Week 24 LOCF Mean (SD) | 7.08 (1.03) | 6.83 (1.04) | 7.93 (1.47) |
| Mean Change from Bsl. (SD) | -0.91 (0.92) | -1.16 (0.99) | -0.05 (1.12) |
| ANCOVA Adjusted Mean (SE) | -0.91 (0.06) | -1.16 (0.07) | -0.05 (0.07) |
| Difference vs PLA+MET | -0.86 (0.09) | -1.11 (0.10) | |
| 95% two-sided CI | [-1.04, -0.67] | [-1.30, -0.92] | |

*2.2.1.5 Combination with metformin (noninferiority to pioglitazone) - CV168025*

A total of 1159 patients were randomized, 587 to muraglitazar 5 mg plus metformin and 574 to pioglitazone 30 mg plus metformin. Of the 1159 patients randomized, 1119 patients were in the primary analysis. The adjusted mean change from baseline in $HbA_{1c}$ for muraglitazar 5 mg+metformin was -1.14% compared to -0.85% for pioglitazone 30 mg+metformin (Table 12). The difference in adjusted mean change from baseline between the two treatment groups was -0.29% with a 95% CI of -0.39% to -0.19%. The upper limit of the 95% CI is less than the 0.25% margin which demonstrated non-inferiority of muraglitazar 5 mg+ metformin compared to pioglitazone 30 mg+metformin. In addition, this CI does not include zero and, therefore, the superiority of muraglitazar 5 mg+metformin was tested. This test resulted in a p-value of <0.01, concluding statistically muraglitazar 5 mg+metformin was superior to pioglitazone 30 mg+metformin in $HbA_{1c}$ change from baseline.

*Table 12 Sponsor's analysis in $HbA_{1c}$ change from baseline - Combination with metformin*

| | MUR 5+MET N=587 | Pio 30+MET N=572 |
|---|---|---|
| n | 569 | 550 |
| Baseline Mean (SD) | 8.12 (0.96) | 8.13 (1.00) |
| Week 24 LOCF Mean (SD) | 6.98 (1.00) | 7.28 (1.09) |
| Mean Change from Bsl. (SD) | -1.14 (0.90) | -0.86 (0.97) |
| ANCOVA Adjusted Mean (SE) | -1.14 (0.04) | -0.85 (0.04) |
| Difference vs Pio 30+Met | -0.29 (0.05) | |
| 95% two-sided CI | [-0.39, -0.19] | |

2.2.2 STATISTICAL METHODOLOGIES

$HbA_{1c}$ change from baseline in $HbA_{1c}$ at Week 24 (LOCF) during the double-blind phase was analyzed using an ANCOVA model with the difference between the post-treatment and baseline value as the dependent variable, with treatment group as the effect and the baseline value as a covariate. Point estimates and two-sided 95% confidence intervals for mean changes from baseline within each treatment group as well as between the muraglitazar 5 mg plus metformin and the pioglitazone 30 mg plus metformin treatment groups were obtained from the ANCOVA model.

Site was not considered as a fixed factor in the model because of the small number of patients at each site. However, the sponsor should have considered geographical region as a fixed effect in the model.

The treatment-by-baseline interaction was tested at the 0.10 level of significance. The Koch-Gansky sequential testing procedure was used to provide an overall significance level of 0.05; comparisons were performed at a two-sided level ($a = 0.05$). The first comparison was between the highest dose of muraglitazar and the control treatment group. If this comparison was statistically significantly different, then a comparison between the next highest muraglitazar dose treatment group and the control treatment group was performed. Additionally, 2 sensitivity analyses on change from baseline in $HbA_{1c}$ were carried out, one including patients who were discontinued from the study prior to receiving at least 6 weeks of double-blind treatment and the other including patients who had both a baseline and a Week 24 $HbA_{1c}$ value (i.e. completer's analysis).

2.2.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

*2.2.3.1 Dose Ranging Study - CV168006*

This was a multicenter, randomized, double-blind, dose ranging, dose comparison, controlled, six parallel groups trial of 5 doses of muraglitazar (0.5, 1.5, 5, 10, 20 mg) and a dose of pioglitazone (15 mg) in patients. Patients should have either been drug naïve or should not have received any antihyperglycemic therapy for more than three consecutive days or a total of seven non-consecutive days during the four to six weeks prior to screening.

Drug naïve was defined as any subject who had received treatment for diabetes for less than one month.

A total of 1479 patients were randomized, 793 at 176 sites located in the US and Puerto Rico, 405 at 83 sites in 9 countries in Europe and 281 at 34 sites in 5 additional countries.

The primary objective was to compare, after 24 weeks of oral administration of double-blind treatment, the $HbA_{1c}$ change from baseline achieved with the highest dose and subsequent doses of muraglitazar versus the lowest dose of muraglitazar in patients with type 2 diabetes.

The primary efficacy variable was $HbA_{1c}$ change from baseline at Week 24 or the last post baseline measurement prior to rescue medication. The primary comparisons were between the highest dose (20 mg) and subsequent doses of muraglitazar (10 mg, 5 mg, 1.5 mg) versus the lowest dose of muraglitazar (0.5 mg).

The Koch-Gansky sequential testing procedure starting with the 20mg vs. 0.5mg comparison was used to provide an overall alpha level of 0.05. The analysis of covariance model used baseline as the covariate.

The key inclusion criteria were men and women 18-70 years of age with established type 2 diabetes, $HbA_{1c}$ >7.0% and =10.0%, Body Mass Index =41 kg/m$^2$ and TG=600 mg/dL.

Patient Disposition

The study randomized 1479 patients to the double-blind therapy. A total 1136 patients were in the primary analysis population of those 1032 patients completed the 24 week treatment phase. Table 13 displays number of patients in the analysis population, Table 14 the disposition of patients with reasons for discontinuation.

*Table 13 Number of patients included in key analyses – Dose ranging study*

| | Muraglitazar | | | | | Pio | Total |
|---|---|---|---|---|---|---|---|
| | 0.5mg | 1.5mg | 5mg | 10mg | 20mg | 15 mg | |
| Randomized | 236 | 259 | 245 | 249 | 239 | 251 | 1479 |
| Treated | 236 | 259 | 245 | 249 | 237 | 251 | 1477 |
| Evaluable | 217 (92%) | 248 (96%) | 228 (93%) | 232 (93%) | 222 (93%) | 235 (94%) | 1382 |
| Rescued | 93 (39%) | 82 (32%) | 48 (20%) | 24 (10%) | - | 79 (31%) | 326 |
| Prim. Analysis | 216 (92%) | 235 (91%) | 227 (93%) | 231 (93%) | 227 (95%) | | 1136 |

*Table 14 Patient disposition – Dose ranging study*

| | Muraglitazar | | | | | Pioglitazone |
|---|---|---|---|---|---|---|
| . | 0.5mg n=236 | 1.5mg n=259 | 5mg n=245 | 10mg n=249 | 20mg n=237 | 15 mg 251 |
| Adverse Event | 4 | 11 | 9 | 23 | 29 | 12 |
| Patient withdrew consent | 16 | 18 | 12 | 14 | 12 | 10 |
| Lost to follow up | 8 | 4 | 6 | 2 | 4 | 5 |
| Rescue/Treatment failure | 61 | 41 | 23 | 9 | 18 | 58 |
| Non compliance | 0 | 5 | 1 | 3 | 0 | 6 |
| Death | 0 | 0 | 0 | 1 | 1 | 0 |
| Patients no longer meets study criteria | 2 | 4 | 2 | 0 | 3 | 1 |
| Other | 2 | 1 | 1 | 2 | 1 | 2 |

The number of patients who withdrew due to adverse events was greater in patients treated with 10 mg and 20 mg muraglitazar.

Baseline demographic and characteristics were similar among the treatment groups (Table 15).

*Table 15 Baseline demographic and characteristics*

| | | Muraglitazar | | | | | | | | | | Pioglitazone | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.5 mg n=236 | | 1.5 mg n=259 | | 5 mg n=245 | | 10 mg n=249 | | 20 mg n=237 | | 15 mg n=251 | |
| Age, years | Mean (SD) | 54.4 | (9.0) | 53.8 | (10.1) | 54.3 | (9.6) | 54.7 | (10.1) | 53.9 | (8.9) | 53.5 | (9.2) |
| Gender, n (%) | Male | 105 | (44) | 113 | (44) | 100 | (41) | 121 | (49) | 95 | (40) | 106 | (42) |
| | Female | 131 | (56) | 146 | (56) | 145 | (59) | 128 | (51) | 142 | (60) | 145 | (58) |
| Race, n (%) | White | 188 | (80) | 209 | (81) | 207 | (84) | 203 | (82) | 193 | (81) | 204 | (81) |
| | Black | 16 | (7) | 19 | (7) | 15 | (6) | 16 | (6) | 12 | (5) | 19 | (8) |
| | Other | 32 | (14) | 31 | (12) | 23 | (9) | 30 | (12) | 32 | (14) | 28 | (11) |
| $HbA_{1c}$ (%) | n | 235 | | 258 | | 244 | | 249 | | 237 | | 250 | |
| | Mean (SD) | 8.26 | (1.13) | 8.20 | (1.08) | 8.25 | (1.04) | 8.18 | (1.06) | 8.18 | (1.12) | 8.36 | (1.14) |
| Weight (kg) | Mean (SD) | 88.3 | (16.9) | 89.1 | (17.4) | 89.1 | (17.0) | 88.8 | (18.0) | 90.9 | (16.9) | 90.4 | (17.0) |
| Years with diabetes | n | 236 | | 259 | | 243 | | 249 | | 237 | | 249 | |
| | Mean (SD) | 3.63 | (4.56) | 3.03 | (3.56) | 3.20 | (4.31) | 3.79 | (4.87) | 3.13 | (3.99) | 3.46 | (3.96) |

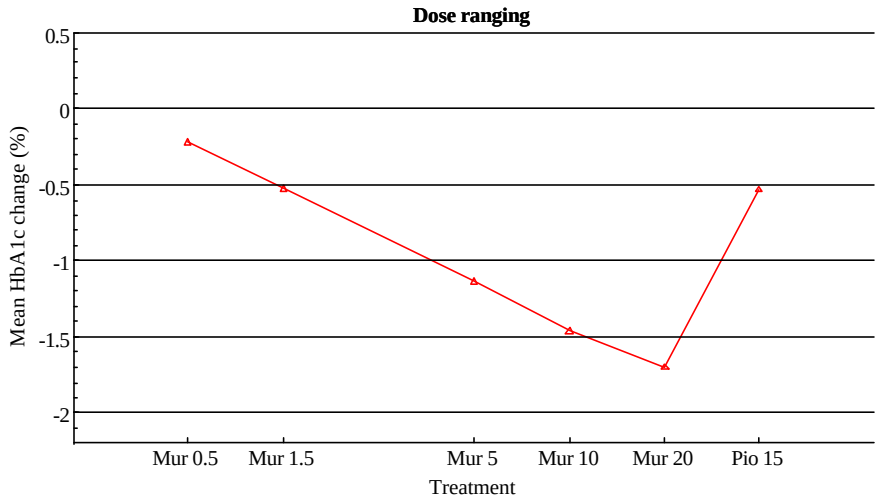
Efficacy analysis:

The primary efficacy variable was $HbA_{1c}$ (%) change from baseline using ANCOVA model with treatment group as the fixed effect and baseline as a covariate. The sponsor's sensitivity analysis included all patients with one baseline and at least one follow up of $HbA_{1c}$ which this reviewer presents as the intent-to-treat analysis (Table 16). Figure 10 displays the mean $HbA_{1c}$ change from baseline by treatment doses. Muraglitazar doses 20 mg, 10 mg, 5 mg and 1.5 mg were all significantly different from muraglitazar 0.5 mg in $HbA_{1c}$ change from baseline in a dose dependent relationship.

*Table 16 Sponsor's sensitivity analysis of the $HbA_{1c}$ change from baseline – Dose ranging*

| | Mur 0.5 mg | Mur 1.5 mg | Mur 5 mg | Mur 10 mg | Mur 20 mg |
|---|---|---|---|---|---|
| n | 223 | 245 | 236 | 240 | 233 |
| Baseline Mean (SD) | 8.21 (1.11) | 8.16 (1.04) | 8.26 (1.04) | 8.17 (1.05) | 8.17 (1.12) |
| Week 24 LOCF Mean (SD) | 7.99 (1.62) | 7.64 (1.55) | 7.12 (1.45) | 6.71 (1.24) | 6.46 (1.32) |
| Mean Change from Bsl. (SD) | -0.22 (1.08) | -0.52 (1.14) | -1.14 (1.14) | -1.46 (1.20) | -1.70 (1.19) |
| LSMean (SE) | -0.22 (0.08) | -0.53 (0.07) | -1.12 (0.07) | -1.47 (0.07) | -1.71 (0.07) |
| Difference vs Mur 0.5 mg | | -0.31 (0.11) | -0.91 (0.11) | -1.25 (0.11) | -1.49 (0.11) |
| 95% two-sided CI | | [-0.52, -0.10] | [-1.11, -0.70] | [-1.45, -1.04] | [-1.70, -1.28] |

*Figure 10 Mean $HbA_{1c}$ change from baseline by treatment – ITT*

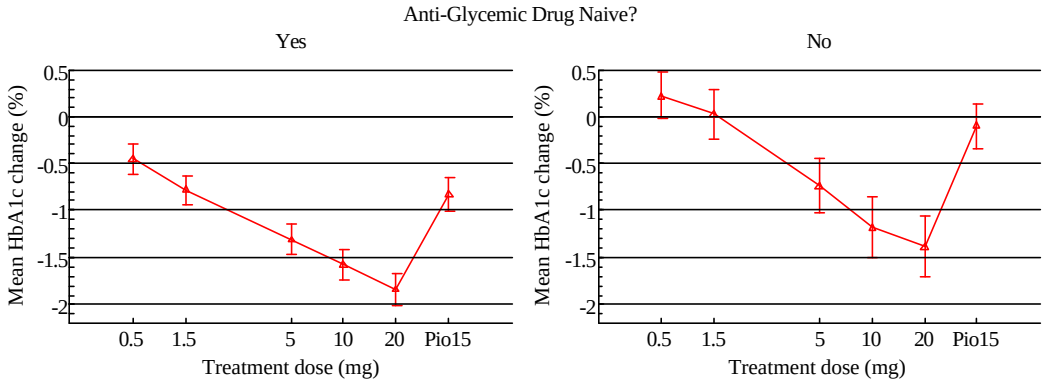



One third of patients were not naïve to antiglycemic medication. Table 17 and Figure 11 display the means stratified by naïve patients (Yes) or non naïve patients (No).

*Table 17 Mean $HbA_{1c}$ change from baseline by stratum – Dose ranging*

| | Mur 0.5 mg | | Mur 1.5 mg | | Mur 5 mg | | Mur 10 mg | | Mur 20 mg | | Pio 15 mg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Naïve | | | | | | | | | | | | |
| n | 146 | | 166 | | 164 | | 168 | | 162 | | 144 | |
| Baseline Mean (SD) | 8.00 | (1.00) | 8.01 | (0.99) | 8.10 | (1.01) | 8.05 | (1.03) | 8.02 | (1.04) | 8.04 | (1.04) |
| Endpoint Mean (SD) | 7.55 | (1.30) | 7.23 | (1.32) | 6.80 | (1.19) | 6.47 | (0.96) | 6.18 | (0.99) | 7.21 | (0.99) |
| Mean Change from Bsl. (SD) | -0.46 | (0.98) | -0.78 | (1.02) | -1.31 | (1.05) | -1.58 | (1.08) | -1.84 | (1.06) | -0.83 | (1.10) |
| LSM change from Bsl (SE) | -0.50 | (0.09) | -0.82 | (0.09) | -1.33 | (0.09) | -1.61 | (0.09) | -1.88 | (0.09) | -0.86 | (0.09) |
| Non naïve | | | | | | | | | | | | |
| n | 77 | | 79 | | 71 | | 72 | | 71 | | 96 | |
| Baseline Mean (SD) | 8.60 | (1.20) | 8.48 | (1.07) | 8.62 | (1.02) | 8.44 | (1.06) | 8.50 | (1.23) | 8.79 | (1.06) |
| Endpoint Mean (SD) | 8.83 | (1.83) | 8.51 | (1.66) | 7.88 | (1.72) | 7.26 | (1.60) | 7.12 | (1.70) | 8.70 | (1.71) |
| Mean Change from Bsl. (SD) | 0.22 | (1.13) | 0.02 | (1.20) | -0.74 | (1.27) | -1.18 | (1.41) | -1.38 | (1.40) | -0.10 | (1.18) |
| LSM change from Bsl (SE) | +0.3 | (0.13) | 0.07 | (0.12) | -0.67 | (0.13) | -1.14 | (0.13) | -1.33 | (0.13) | +0.01 | (0.11) |

*Figure 11 Mean $HbA_{1c}$ change from baseline by treatment in naïve or non naïve patients*




Treatment-by-baseline interaction was significant (p=0.02) when muraglitazar 1.5 mg and 5 mg were in the analysis (Fig. 12). Treatment-by-naïve-by-baseline interaction was significant (p<0.01). Figure 13 shows the positive slopes for the non naïve patients and negative slopes for the naïve patients.

*Figure 12 $HbA_{1c}$ change by baseline $HbA_{1c}$*

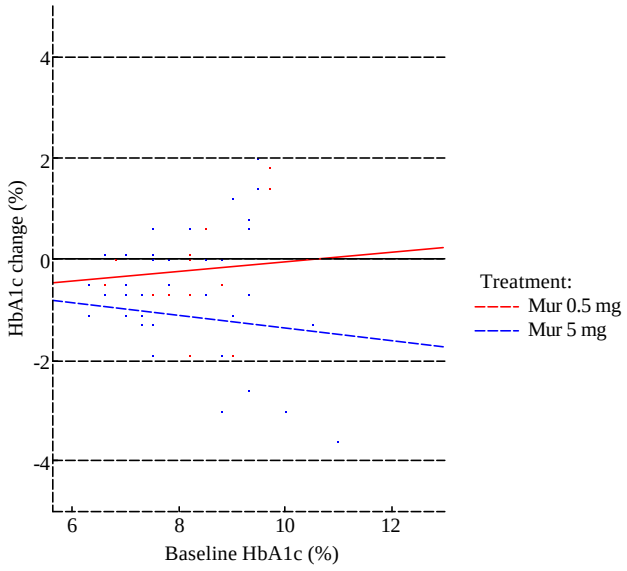
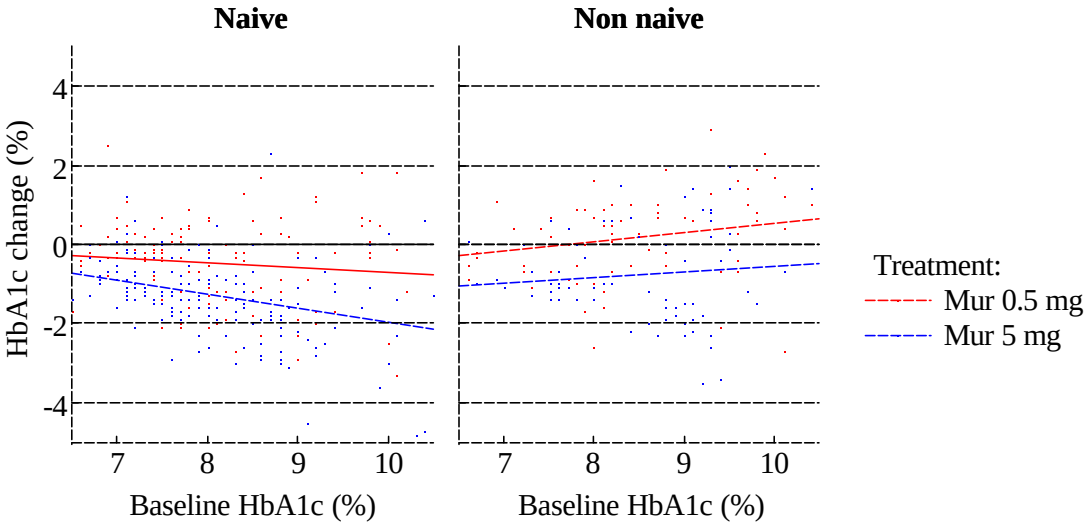


*Figure 13 $HbA_{1c}$ change by baseline $HbA_{1c}$ in naïve or non naïve patients*




Subgroup analysis:
The treatment-by-gender and treatment-by-race interactions were quantitative in nature (p=0.06, 0.10) when muraglitazar 0.5 mg and 5 mg were in the analysis (Fig 14 and 15). The treatment-by-age group interaction (=65, >65) was not significant (Fig 16).

*Figure 14 Mean $HbA_{1c}$ change from baseline by treatment dose - gender*

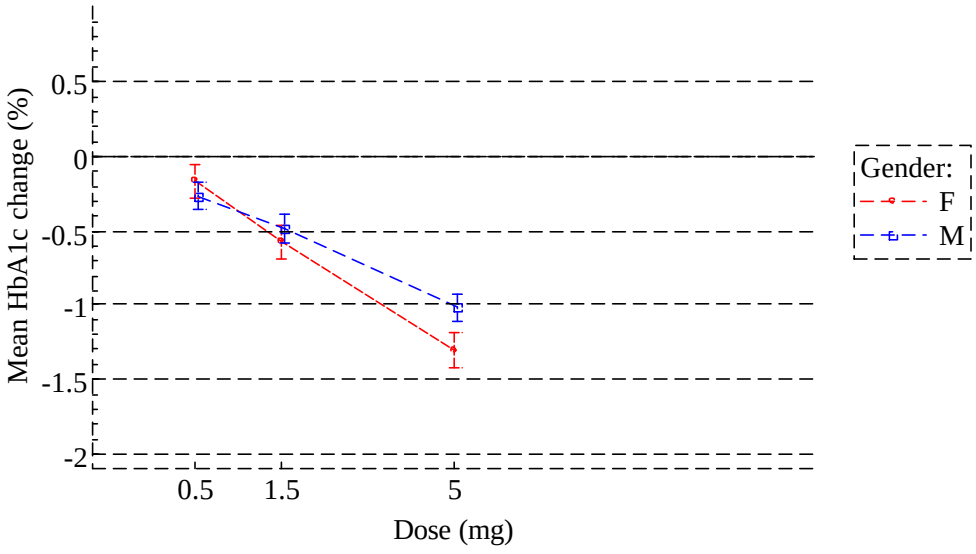


*Figure 15 Mean $HbA_{1c}$ change from baseline by treatment dose – Race*

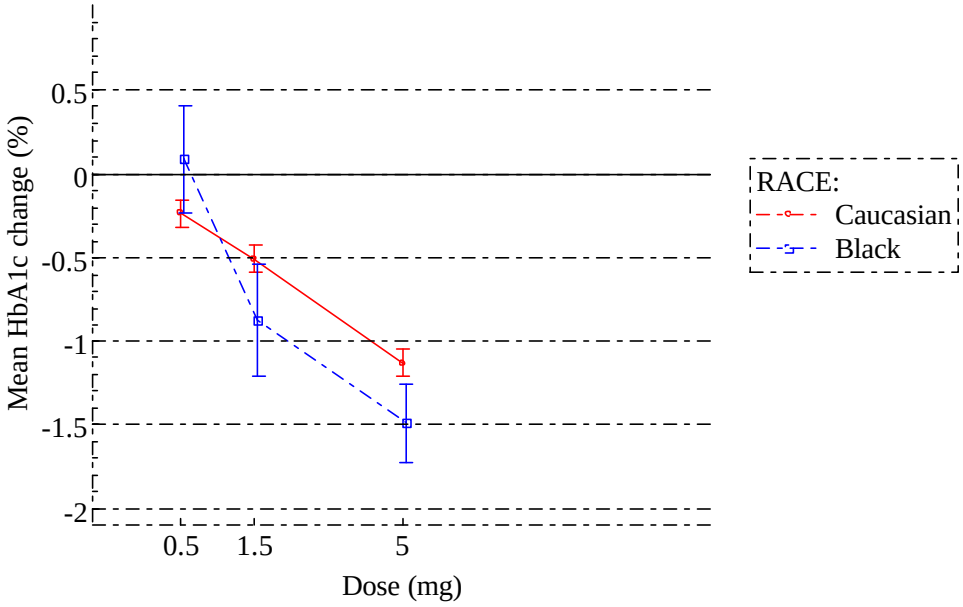
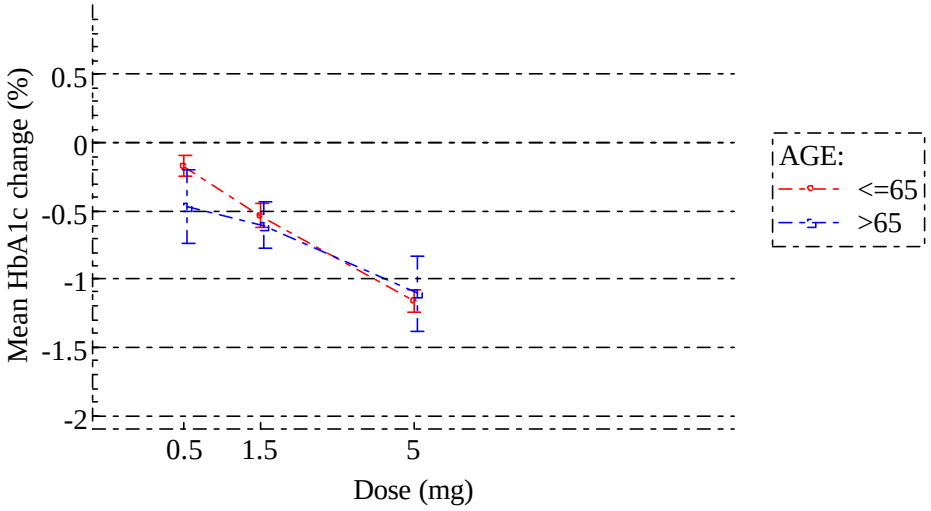



*Figure 16 $HbA_{1c}$ change from baseline by treatment – Age group*



### *2.2.3.2 Monotherapy – CV168018*

This randomized, 3 parallel groups, double-blind, placebo-controlled, multicenter phase 3 study compared 2 doses of muraglitazar to placebo. Patients were drug naïve and should not have received any anti-hyperglycemic therapy for more than 3 consecutive days or a total of 7 non-consecutive days during the 4 to 6 weeks prior to screening. Drug-naïve patients were defined as patients who had never received treatment for diabetes or had received treatment for less than one month. A total of 127 sites (83 in the US and Puerto Rico and 44 sites in 4 other countries) screened patients and 123 sites received study drug. Of the 340 patients randomized 255 (75%) completed the study. Table 18 displays patient disposition during the double-blind phase.

*Table 18 Patient disposition – Monotherapy*

| . | Mur 2.5mg n=111 | | Mur 5mg n=114 | | Placebo n=115 | | Total n=340 | |
|---|---|---|---|---|---|---|---|---|
| Completed | 90 | (81.1%) | 92 | (80.7%) | 73 | (63.5%) | 255 | (75.0%) |
| Adverse event | 3 | (2.7%) | 4 | (3.5%) | 3 | (2.6%) | 14 | (4.1%) |
| Lack of efficacy | 9 | (8.1%) | 10 | (8.7%) | 32 | (27.8%) | 51 | (15.0%) |
| Patient withdrew consent | 3 | (2.7%) | 6 | (5.3%) | 5 | (4.4%) | 14 | (4.1%) |
| Lost to follow up | 4 | (3.6%) | 2 | (1.8%) | 0 | (0%) | 6 | (1.8%) |
| Patients no longer meets study criteria | 0 | (0%) | 0 | (0%) | 1 | (0.9%) | 1 | (0.3%) |
| Non compliance | 1 | (0.9%) | 0 | (0%) | 1 | (0.9%) | 2 | (0.6%) |
| Other | 1 | (0.9%) | 0 | (0%) | 0 | (0%) | 1 | (0.3%) |

Table 19 displays baseline demographics and characteristics.

*Table 19 Demographics and baseline characteristics - Monotherapy*

| | Mur 2.5 mg | Mur 5 mg | Placebo |
|---|---|---|---|
| | 111 | 114 | 115 |
| <65 years | 96(86.5%) | 100(87.7%) | 109(94.8%) |
| =65 years | 15(13.5%) | 14(12.3%) | 6(5.2%) |
| Age (years) | | | |
| Mean (SD) | 52.1(10.6) | 52.8(9.7) | 50.4(10.0) |
| Gender, n (%) | | | |
| Male | 65(58.6%) | 61(53.5%) | 53(46.1%) |
| Female | 46(41.4%) | 53(46.5%) | 62(53.9%) |
| Race, n (%) | | | |
| White | 89(80.2%) | 90(78.9%) | 86(74.8%) |
| Black | 6(5.4%) | 6(5.3%) | 7(6.1%) |
| Other | 16(14.4%) | 18(15.8%) | 22(19.1%) |
| $HbA_{1c}$ (%) | | | |
| Mean (SD) | 8.04(1.05) | 7.87(0.98) | 7.97(1.04) |
| Weight (kg) | | | |
| Mean (SD) | 90.5(18.9) | 88.6(20.3) | 88.2(21.5) |
| Years with diabetes | | | |
| Mean (SD) | 1.88(3.31) | 2.37(3.50) | 2.26(3.94) |

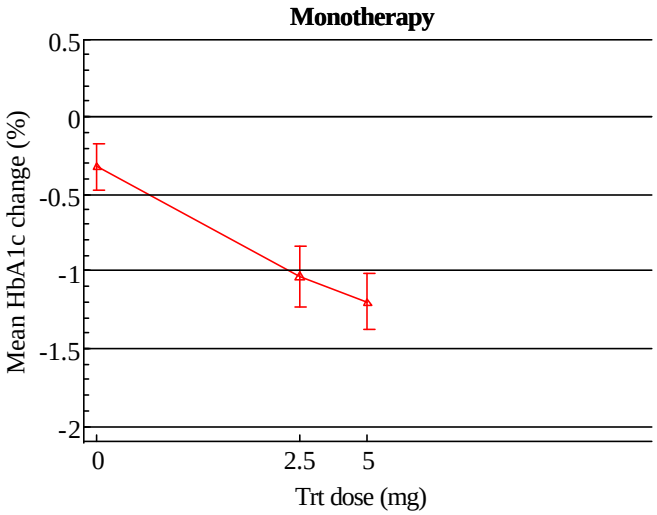
Primary Efficacy Analysis – $HbA_{1c}$ Change from baseline

Both muraglitazar 2.5 mg and muraglitazar 5 mg were statistically significantly superior to placebo in $HbA_{1c}$ change from baseline. The differences from placebo were -0.70% for the 2.5 mg group and -0.90% for the 5 mg group (Table 20, Fig. 17).

*Table 20 Mean $HbA_{1c}$ change from baseline – ITT, Monotherapy*

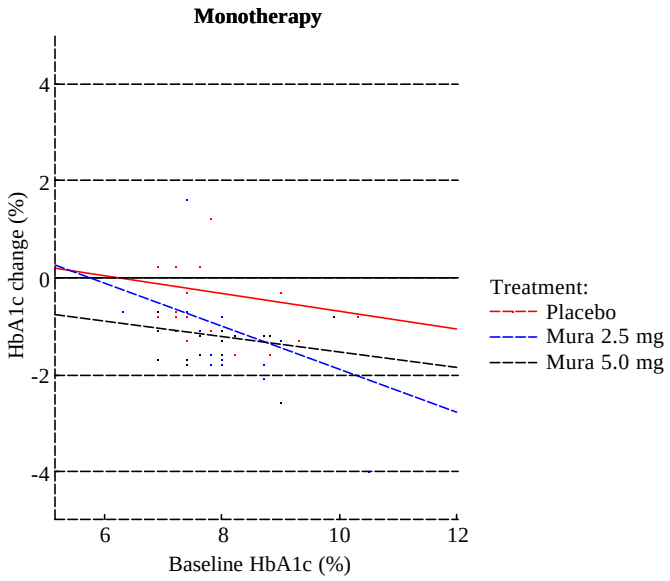
| | Mur 2.5 mg | Mur 5 mg | Placebo |
|---|---|---|---|
| n | 111 | 114 | 115 |
| Baseline Mean (SD) | 8.05(1.03) | 7.88(0.99) | 8.00(1.04) |
| Endpoint Mean (SD) | 7.02(1.09) | 6.68(1.29) | 7.68(1.17) |
| Mean Change from Bsl. (SD) | -1.04(1.03) | -1.20(0.99) | -0.32(0.82) |
| Adjusted Change from Baseline (SE) | -1.02(0.09) | -1.22(0.09) | -0.32(0.09) |
| Difference in Adjusted Change from Baseline vs PLA | -0.70(0.12) | -0.90(0.12) | |
| 95% 2-sided CI | [ -0.94, -0.45] | [ -1.15, -0.66] | |
| P value | <0.0001 | <0.0001 | |

*Figure 17 Mean $HbA_{1c}$ change from baseline - Monotherapy*




The overall treatment-by-baseline interaction was significant (p=0.03). The regression line of $HbA_{1c}$ change from baseline by baseline $HbA_{1c}$ for 2.5 mg group was steeper than placebo group and the 5.0 mg group (Fig 18).

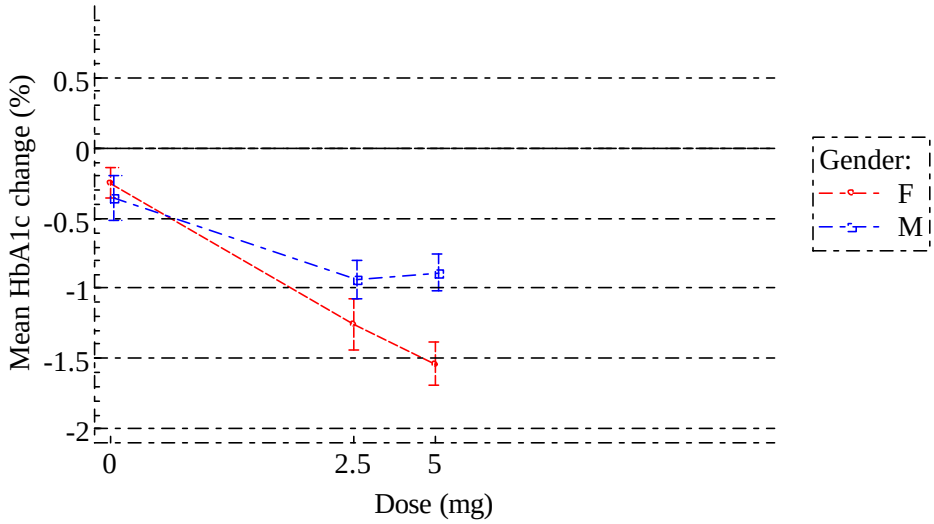
*Figure 18 $HbA_{1c}$ change from baseline by baseline $HbA_{1c}$ - Monotherapy*




Subgroup analysis:

The treatment-by-gender interaction was significant (p=0.04) for placebo and 5 mg muraglitazar (Figure 19). The mean (SE) $HbA_{1c}$ change from baseline difference between 5 mg muraglitazar and placebo was -1.17% (0.17) for female patients and -0.68% (0.17) for male patients. No treatment-by-subgroup interaction was detected for race and age group. The majority of patients were Caucasian (78%) and most patients were =65 years in age (90%).

*Figure 19 Mean $HbA_{1c}$ change from baseline by gender - Monotherapy*



*2.2.3.3 Add on Sulfonylurea – CV168021*

This was a multicenter, randomized, double-blind, 3 parallel groups, placebo-controlled, Phase 3 trial of 2 doses of muraglitazar (once daily) added on as combination therapy with glyburide 15 mg (once daily), in patients with type 2 diabetes who had inadequate glycemic control. Patients were required to receive glyburide =10 mg to < 20 mg or receive at least a half-maximal labeled dose of sulfonylurea therapy. The primary objective was to compare, after 24 weeks of treatment with each dose of muraglitazar plus glyburide 15 mg versus placebo plus glyburide 15 mg in patients with type 2 diabetes who have inadequate glycemic control ($HbA_{1c}$ =7% and =10%). Eligible patients were to receive open-label glyburide 15 mg for 2 weeks and continue to receive glyburide 15 mg for 2 weeks in a single-blind, dietary and exercise placebo lead-in phase (Period A). In Period B, patients were randomized to once daily muraglitazar 2.5 mg, 5 mg or placebo for 24 weeks. Muraglitazar titration was not allowed. Glyburide 15 mg down-titration was allowed during Period B.

A total of 162 sites randomized 583 patients. Of the 583 patients, 464 (80%) patients completed the study. Table 21 displays patient disposition.

*Table 21 Patient disposition – Add on glyburide*

| | Mur 2.5 + Gly n=191 | | Mur 5 + Gly n=193 | | Placebo + Gly n=199 | | Total n=583 | |
|---|---|---|---|---|---|---|---|---|
| Completed | 159 | (83.2%) | 166 | (86.0%) | 139 | (69.8%) | 464 | (79.6%) |
| Discontinued | 32 | (16.8%) | 27 | (14.0%) | 60 | (30.2%) | 119 | (20.4%) |
| Adverse event | 7 | (3.7%) | 11 | (5.7%) | 4 | (2.0%) | 22 | (3.8%) |
| Lack of efficacy | 9 | (4.7%) | 8 | (4.1%) | 41 | (20.6%) | 58 | (9.9%) |
| Patient withdrew consent | 7 | (3.7%) | 6 | (3.1%) | 8 | (4.0%) | 21 | (3.6%) |
| Lost to follow up | 7 | (3.7%) | 0 | (0.0%) | 2 | (1.0%) | 9 | (1.5%) |
| Other | 1 | (0.5%) | 1 | (0.5%) | 1 | (0.5%) | 3 | (0.5%) |
| Non compliance | 1 | (0.5%) | 0 | (0.0%) | 2 | (1.0%) | 3 | (0.5%) |
| Death | 0 | (0.0%) | 1 | (0.5%) | 0 | (0.0%) | 1 | (0.2%) |
| Pregnancy | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.5%) | 1 | (0.2%) |
| Patients no longer meets study criteria | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.5%) | 1 | (0.2%) |

Table 22 displays demographic and baseline characteristics for the treatment groups.

Baseline $HbA_{1c}$ and body weight was significantly different among groups. The body weight was 88 kg in the placebo patients and 83 kg in the muraglitazar groups and the mean $HbA_{1c}$ was smaller in the muraglitazar 2.5 mg group (7.9%) than in the placebo and the muraglitazar 5 mg groups (8.2%).

*Table 22 Patient demographics and baseline characteristics – Add on glyburide*

| | | Mur 2.5 + Gly n=191 | Mur 5 + Gly n=193 | Placebo + Gly n=199 | Total n=583 |
|---|---|---|---|---|---|
| Age Category | | | | | |
| | < 65 years | 157 (82.2%) | 154 (79.8%) | 172 (86.4%) | 483 (82.8%) |
| | = 65 years | 34 (17.8%) | 39 (20.2%) | 27 (13.6%) | 100 (17.2%) |
| Age (years) | | | | | |
| | Mean (SD) | 54.8 (9.2) | 55.8 (8.8) | 54.7 (9.3) | 55.1 (9.1) |

| | Mur 2.5 + Gly n=191 | Mur 5 + Gly n=193 | Placebo + Gly n=199 | Total n=583 |
|---|---|---|---|---|
| Gender | | | | |
| Male | 104 (54.5%) | 103 (53.4%) | 109 (54.8%) | 316 (54.2%) |
| Female | 87 (45.5%) | 90 (46.6%) | 90 (45.2%) | 267 (45.8%) |
| Race | | | | |
| White | 158 (82.7%) | 160 (82.9%) | 169 (84.9%) | 487 (83.5%) |
| Black | 14 (7.3%) | 18 (9.3%) | 18 (9.0%) | 50 (8.6%) |
| Other | 19 (9.9%) | 15 (7.8%) | 12 (6.0%) | 46 (7.9%) |
| Ethnicity | | | | |
| Hispanic/Latino | 103 (53.9%) | 101 (52.3%) | 102 (51.3%) | 306 (52.5%) |
| Non Hispanic/Latino | 88 (46.1%) | 92 (47.7%) | 97 (48.7%) | 277 (47.5%) |
| Body Mass Index (kg/m$^2$) | | | | |
| Mean (SD) | 30.2 (4.9) | 30.3 (4.5) | 31.2 (5.1) | 30.6 (4.9) |
| Body Weight (kg) | | | | |
| Mean (SD) | 83.3 (19.4) | 82.7 (16.6) | 87.5 (20.1) | 84.5 (18.9) |
| Duration of type 2 diabetes (years) | | | | |
| Mean (SD) | 6.8 (6.4) | 6.7 (5.2) | 6.9 (5.6) | 6.8 (5.7) |
| $HbA_{1c}$ (%) | 7.9 (1.1) | 8.2 (1.1) | 8.2 (1.0) | 8.1 (1.1) |

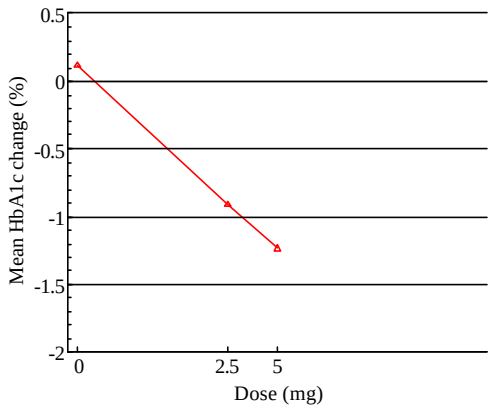
Primary efficacy – $HbA_{1c}$ change from baseline

The placebo group had an increase and the muraglitazar 2.5 mg and 5.0 mg had a decrease of -0.98% and -1.21%, respectively, in $HbA_{1c}$ change from baseline (Table 23, Fig. 20).

*Table 23 $HbA_{1c}$ change from baseline – ITT, Add on glyburide*

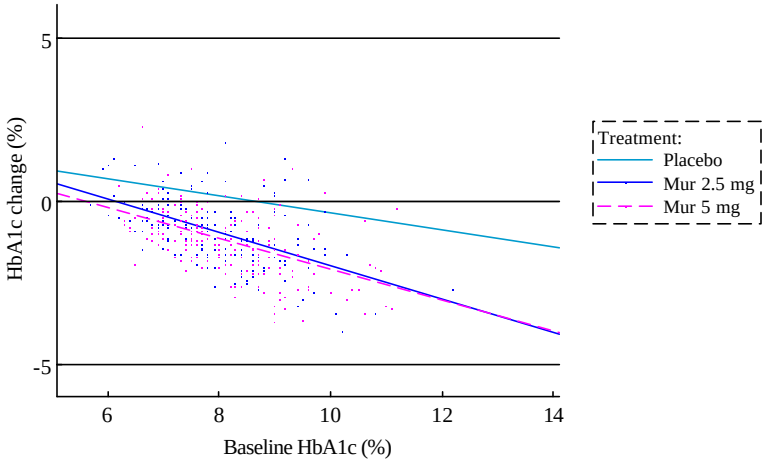
| | Mur 2.5 + Gly n=191 | Mur 5 + Gly n=193 | Placebo + Gly n=199 |
|---|---|---|---|
| n | 179 | 189 | 197 |
| Baseline Mean (SD) | 7.94 (1.09) | 8.17 (1.08) | 8.22 (0.97) |
| Endpoint Mean (SD) | 7.04 (1.00) | 6.94 (1.04) | 8.34 (1.25) |
| Mean Change from Bsl. (SD) | -0.91 (1.02) | -1.23 (1.01) | +0.12 (1.06) |
| ANCOVA Adjusted Mean (SE) | -0.98 (0.07) | -1.21 (0.07) | +0.16 (0.07) |
| Difference vs. Placebo+Gly | -1.14 (0.10) | -1.37 (0.09) | |
| 95% two-sided CI | [-1.33, -0.95] | [-1.55, -1.18] | |
| p value | <0.0001 | <0.0001 | |

*Figure 20 Mean $HbA_{1c}$ change from baseline by dose – Add on glyburide*



The treatment-by-baseline $HbA_{1c}$ interaction was significant (p=0.02). As the regression lines for the two muraglitazar plus glyburide groups did not cross the placebo plus glyburide group regression line the interaction was regarded as quantitative in nature (Fig 21).

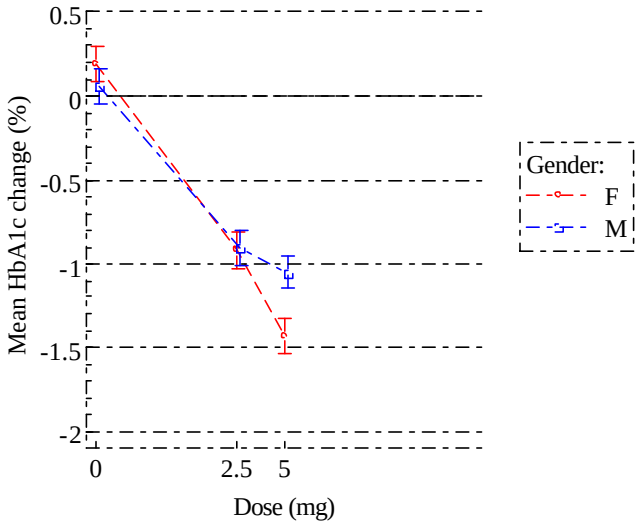
*Figure 21 Regression of $HbA_{1c}$ change from baseline over baseline $HbA_{1c}$*




Subgroup analysis:

Treatment-by-gender interaction was significant (p=0.016). The interaction was quantitative with greater $HbA_{1c}$ reduction in female patients for the 5 mg group (Fig 22).

*Figure 22 Mean $HbA_{1c}$ change from baseline by dose – Add on glyburide*




Treatment-by-race or ethnicity (Hispanic/Latino) or age group (cutoff 65 years) was not significant.

*2.2.3.4 Add on Metformin – CV168022*

This was a multicenter, randomized, double-blind, 3 parallel groups, placebo-controlled, Phase 3 trial of 2 doses of muraglitazar added on as combination therapy with metformin in patients with type 2 diabetes who have inadequate glycemic control defined as HbA1c =7.0% and =10.0% currently treated with at least 1500 mg but not more than 2550 mg of metformin per day for at least 6 weeks prior to screening. The primary objective was to compare after 24 weeks of double-blind treatment, the $HbA_{1c}$ change from baseline with each dose of muraglitazar plus metformin versus placebo plus metformin.

In a 2-week dietary and exercise placebo lead-in phase (Period A), eligible patients were to continue their metformin dose based on using multiples of 500-mg metformin tablets or modified the metformin dose not based on the 500-mg tablet to receive 1500, 2000, or 2500 mg/day. Patients demonstrated a compliance of 80% to 120% with the multiple tablet administration during the placebo lead-in phase were eligible for randomization.

In the 24 week double-blind treatment phase (Period B), patients were randomized to take muraglitazar 2.5 mg, muraglitazar 5 mg or placebo once daily prior to the morning meal. Patients on a stable dose of statin 6 weeks prior to randomization were to continue for the first 12 weeks of the double-blind phase. The randomized muraglitazar dose and the metformin dose continued from placebo run-in were to remain unchanged for Period B.

Patients were allowed to discontinue the double-blind treatment for lack of glycemic control. The criteria were >240 mg/dL for week 6, >220 mg/dL for week 8 and >200 mg/dL for weeks 12, 16, and 20.

The long-term double blind extension (Period C) for up to 1.5 years is ongoing.

A total of 251 sites (144 in the US and Puerto Rico, 49 in 3 countries in Europe, and 58 in 7 other countries) enrolled 678 patients and randomized 652 patients to the double-blind treatment. Of those patients randomized, 527 (81%) completed the 24-week study (Table 24). Premature discontinuation for lack of efficacy were 15%, 6% and 3% mg and for AE 2%, 3% and 4.4% for placebo, muraglitazar 2.5, and muraglitazar 5 mg, respectively.

*Table 24 Patient disposition – Add on metformin*

| . | Mur 2.5 + Met n=233 | | Mur 5 + Met n=205 | | Placebo + Met n=214 | | Total n=652 | |
|---|---|---|---|---|---|---|---|---|
| Completed | 197 | (84.5%) | 179 | (87.3%) | 151 | (70.6%) | 527 | (80.8%) |
| Discontinued | 36 | (15.5%) | 26 | (12.7%) | 63 | (29.4%) | 125 | (19.2%) |
| Adverse event | 7 | (3.0%) | 9 | (4.4%) | 4 | (1.9%) | 20 | (3.1%) |
| Lack of efficacy | 14 | (6.0%) | 7 | (3.4%) | 33 | (15.4%) | 54 | (8.3%) |
| Patient withdrew consent | 7 | (3.0%) | 3 | (1.5%) | 14 | (6.5%) | 24 | (3.7%) |
| Lost to follow up | 4 | (1.7%) | 0 | (0.0%) | 7 | (3.3%) | 11 | (1.7%) |
| Non compliance | 1 | (0.4%) | 3 | (1.5%) | 2 | (0.9%) | 6 | (0.9%) |
| Other | 0 | (0.0%) | 2 | (1.0%) | 2 | (0.9%) | 4 | (0.6%) |
| Patients no longer meets study criteria | 1 | (0.4%) | 1 | (0.5%) | 1 | (0.5%) | 3 | (0.5%) |
| Administrative reason by sponsor | 0 | (0.0%) | 1 | (0.5%) | 0 | (0.0%) | 1 | (0.2%) |
| Death | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.2%) |
| Pregnancy | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.2%) |

The demographic and baseline characteristics were similar among treatment groups (Table 25). Overall most patients were Caucasian (89%) and the mean age was 55 years with a median of 5 years with type 2 diabetes. The mean $HbA_{1c}$ was 8.0% and the mean weight 89 kg.

*Table 25 Demographic and Characteristics of patients – Add on metformin*

| | | Mur 2.5 + Met n=233 | Mur 5 + Met n=205 | Placebo + Met n=214 | Total n=652 |
|---|---|---|---|---|---|
| Age Category | | 233 | 205 | 214 | 652 |
| | < 65 years | 204 (87.6%) | 178 (86.8%) | 180 (84.1%) | 562 (86.2%) |
| | = 65 years | 29 (12.4%) | 27 (13.2%) | 34 (15.9%) | 90 (13.8%) |
| Age (years) | | 233 | 205 | 214 | 652 |
| | Mean (SD) | 54.9 (8.1) | 54.1 (9.2) | 55.9 (8.3) | 55.0 (8.5) |
| Gender | | | | | |
| | Male | 132 (56.7%) | 116 (56.6%) | 111 (51.9%) | 359 (55.1%) |
| | Female | 101 (43.3%) | 89 (43.4%) | 103 (48.1%) | 293 (44.9%) |
| Race | | | | | |
| | White | 205 (88.0%) | 180 (87.8%) | 195 (91.1%) | 580 (89.0%) |
| | Black | 16 (6.9%) | 13 (6.3%) | 9 (4.2%) | 38 (5.8%) |
| | Other | 12 (5.2%) | 12 (5.9%) | 10 (4.7%) | 34 (5.2%) |
| Ethnicity | | | | | |
| | Hispanic/Latino | 72 (30.9%) | 68 (33.2%) | 62 (29.0%) | 202 (31.0%) |
| | Non Hispanic/Latino | 161 (69.1%) | 137 (66.8%) | 152 (71.0%) | 450 (69.0%) |
| Body Weight (kg) | | | | | |
| | Mean (SD) | 90.0 (18.8) | 89.0 (19.2) | 88.7 (17.4) | 89.3 (18.5) |
| Body Mass Index ($kg/m^2$) | n | 233 | 205 | 214 | 652 |
| | Mean (SD) | 31.4 (5.0) | 31.3 (4.8) | 31.3 (5.2) | 31.3 (5.0) |
| Duration of type 2 diabetes (years) | n | 233 | 204 | 214 | 651 |
| | Mean (SD) | 6.2 (4.9) | 5.9 (5.3) | 5.3 (4.7) | 5.8 (5.0) |
| | Median | 5.0 | 5.0 | 4.0 | 4.7 |
| | Range | 0.0 - 25.3 | 0.0 - 29.0 | 0.1 - 33.0 | 0.0 - 33.0 |
| $HbA_{1c}$ (%) | | | | | |
| | Mean (SD) | 8.0 (1.0) | 8.0 (1.0) | 8.0 (1.0) | 8.0 (1.0) |
| | Median | 7.9 | 7.9 | 7.7 | 7.8 |
| | Range | 6.3 - 11.5 | 5.7 - 11.1 | 6.2 - 11.0 | 5.7 - 11.5 |

Primary efficacy variable – $HbA_{1c}$ (%) change from baseline

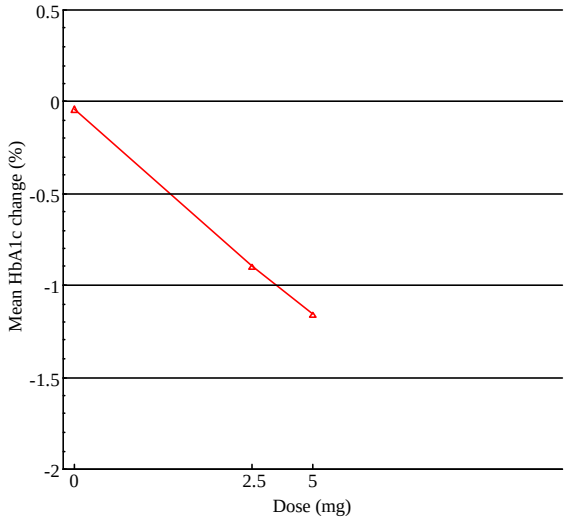
The placebo subtracted difference in $HbA_{1c}$ was -0.9% for muraglitazar 2.5 mg and -1.1 for muraglitazar 5 mg. The differences were statistically significant ($p<0.01$) (Table 26, Fig 23).

*Table 26 $HbA_{1c}$ change from baseline – ITT, Add on glyburide*

| | | Mur 2.5 + Met n=191 | Mur 5 + Met n=193 | Placebo + Met n=199 |
|---|---|---|---|---|
| | n | 226 | 199 | 203 |
| Baseline Mean | (SD) | 8.00 (0.99) | 7.99 (0.99) | 7.99 (1.02) |

| | Mur 2.5 + Met n=191 | Mur 5 + Met n=193 | Placebo + Met n=199 |
|---|---|---|---|
| Endpoint Mean (SD) | 7.10 (1.04) | 6.83 (1.03) | 7.94 (1.47) |
| ANCOVA Adjusted Mean (SE) | -0.90 (0.06) | -1.16 (0.07) | -0.04 (0.07) |
| Difference vs. Placebo+Met | -0.85 (0.09) | -1.12 (0.10) | |
| 95% two-sided CI | [-1.04, -0.67] | [-1.30, -0.93] | |
| p value | <0.0001 | <0.0001 | |

*Figure 23 Mean $HbA_{1c}$ change from baseline by treatment group – Add on metformin*




Subgroup analysis:

The treatment-by-gender and treatment-by-ethnicity interactions were significant. Figure 24 displays the female patients had a greater reduction than male patients in $HbA_{1c}$ reduction for the muraglitazar 2.5 mg-treated patients.

*Figure 24 Mean $HbA_{1c}$ change from baseline by dose and gender – Add on metformin*

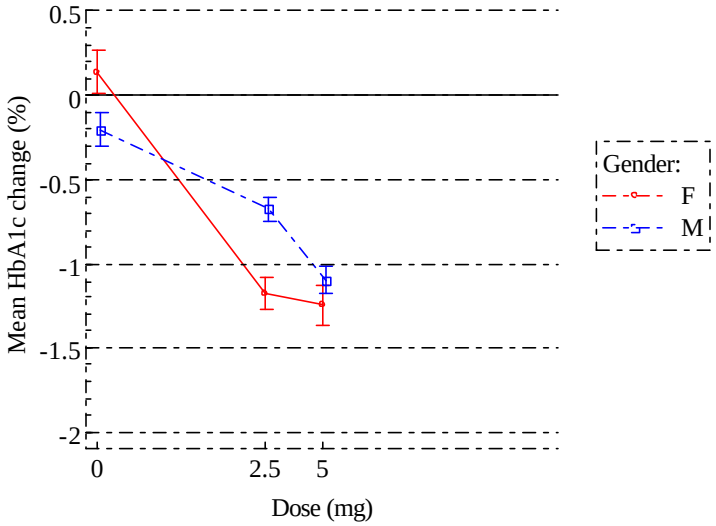
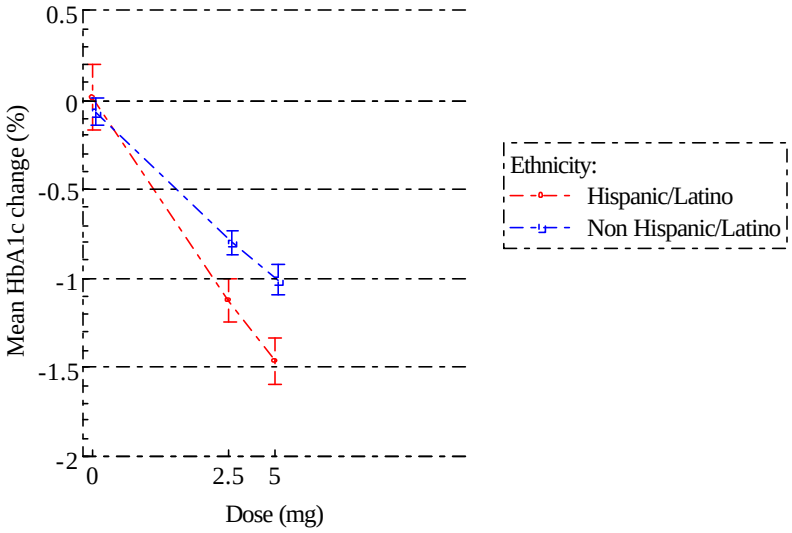



Figure 25 shows that the Hispanic/Latino patients had a greater reduction of $HbA_{1c}$ than the non Hispanic/Latino patients for both muraglitazar treatment groups.

*Figure 25 Mean $HbA_{1c}$ change from baseline by dose and ethnicity – Add on metformin*




*2.2.3.5 Pioglitazone 30 mg controlled Add on Metformin – CV168025*

The study was a multicenter, randomized, double-blind, parallel group, active controlled, Phase 3 trial of muraglitazar 5 mg added on with metformin compared to pioglitazone 30 mg added on with metformin in patients with type 2 diabetes who had inadequate glycemic control (=HbA1c 7.0% and =10.0%) while on a stable dose of metformin 1500 mg to 2550 mg per day for at least 6 weeks prior to screening. The 3 phases of the design is similar to study CV168022 except the extension phase is 26 weeks.

A total of 234 study sites (121 in the US and Puerto Rico, 55 in 7 countries in Europe, and 58 in 5 countries in the rest of the world) enrolled 1202 patients and randomized 1159 patients to double-blind treatment. Of the 1159 patients who were randomized, 1004 (87%) completed the 24-week treatment phase, and 155 discontinued prematurely. The discontinuation for lack of efficacy was 6.3% and 3.1% and for AE was 1.4% and 2.6% for pioglitazone 30 mg and muraglitazar 5.0 mg, respectively (Table 27).

*Table 27 Patient disposition – Active control pioglitazone 30 mg*

| . | Mur 5 + Met n=587 | | Pio 30 + Met n=572 | | Total n=1159 | |
|---|---|---|---|---|---|---|
| Completed | 522 | (88.9%) | 482 | (84.3%) | 1004 | (86.6%) |
| Discontinued | 65 | (11.1%) | 90 | (15.7%) | 155 | (13.4%) |
| Adverse event | 15 | (2.6%) | 8 | (1.4%) | 23 | (2.0%) |
| Lack of efficacy | 18 | (3.1%) | 36 | (6.3%) | 54 | (4.7%) |
| Patient withdrew consent | 16 | (2.7%) | 30 | (5.2%) | 46 | (4.0%) |
| Lost to follow up | 7 | (1.2%) | 7 | (1.2%) | 14 | (1.2%) |
| Non compliance | 4 | (0.7%) | 4 | (0.7%) | 8 | (0.7%) |
| Patients no longer meets study criteria | 2 | (0.3%) | 4 | (0.7%) | 6 | (0.5%) |
| Death | 2 | (0.3%) | 0 | (0.0%) | 2 | (0.2%) |
| Pregnancy | 1 | (0.2%) | 1 | (0.2%) | 2 | (0.2%) |

Baseline characteristics were similar between the 2 treatment groups. Ninety percent of patients were Caucasian and 83% were non Hispanic/Latino in ethnicity. Mean age was 55 years with a median duration of type 2 diabetes for 4 to 5 years. The mean $HbA_{1c}$ at baseline was 8.1% (Table 28).

*Table 28 Demographic and Characteristics of patients – Active control Pioglitazone 30 mg*

| | Mur 5 + Met n=587 | Pio 30 + Met n=572 | Total n=1159 |
|---|---|---|---|
| Age Category | | | |
| < 65 years | 489 (83.3%) | 492 (86.0%) | 981 (84.6%) |
| = 65 years | 98 (16.7%) | 80 (14.0%) | 178 (15.4%) |
| Age (years) | | | |
| Mean (SD) | 55.3 (8.6) | 54.1 (9.1) | 54.7 (8.9) |
| Sex | | | |
| Male | 269 (45.8%) | 280 (49.0%) | 549 (47.4%) |
| Female | 318 (54.2%) | 292 (51.0%) | 610 (52.6%) |
| Race | | | |
| White | 526 (89.6%) | 514 (89.9%) | 1040 (89.7%) |
| Black | 49 (8.3%) | 40 (7.0%) | 89 (7.7%) |
| Other | 12 (2.0%) | 18 (3.1%) | 30 (2.6%) |
| Ethnicity | | | |
| Hispanic/Latino | 88 (15.0%) | 107 (18.7%) | 195 (16.8%) |
| Non Hispanic/Latino | 499 (85.0%) | 465 (81.3%) | 964 (83.2%) |
| Body Mass Index ($kg/m^2$) | | | |
| Mean (SD) | 32.0 (4.6) | 32.0 (4.6) | 32.0 (4.6) |
| Body Weight (kg) | | | |
| Mean (SD) | 90.2 (17.4) | 91.0 (17.2) | 90.6 (17.3) |

| | | | | |
|---|---|---|---|---|
| Duration of type 2 diabetes (years) | | | | |
| | Mean (SD) | 6.0 (5.0) | 5.8 (5.1) | 5.9 (5.0) |
| | Median | 5.0 | 4.2 | |
| $HbA_{1c}$ (%) | | 586 | 572 | 1158 |
| | Mean (SD) | 8.1 (1.0) | 8.1 (1.0) | 8.1 (1.0) |

Primary efficacy variable – $HbA_{1c}$ (%) change from baseline

The adjusted mean $HbA_{1c}$ change from baseline was -1.14% for muraglitazar 5 mg and -0.84% for pioglitazone 30 mg. The -0.2% upper limit of the 2-sided confidence interval was within the 0.25% noninferiority margin (Table 29).

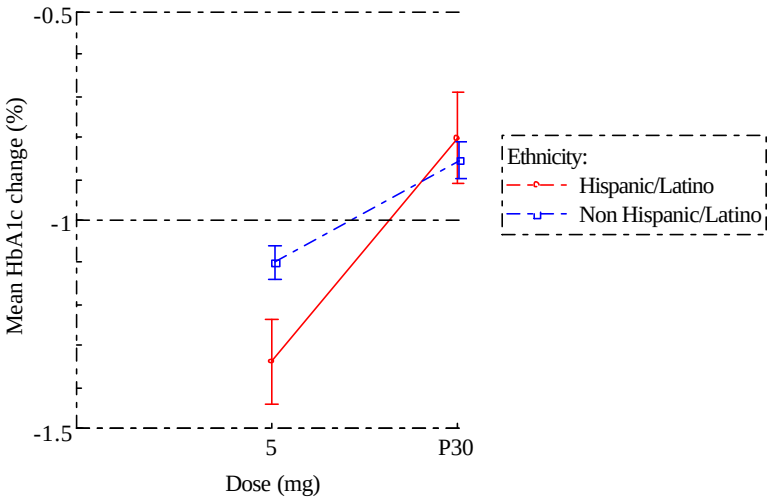
*Table 29 $HbA_{1c}$ change from baseline – ITT, Add on glyburide*

| | Mur 5 + Met n=191 | Pio 35 + Met n=193 |
|---|---|---|
| n | 571 | 561 |
| Baseline Mean (SD) | 8.12(0.97) | 8.13(1.00) |
| Endpoint Mean (SD) | 6.98(1.00) | 7.29(1.09) |
| ANCOVA Adjusted Mean (SE) | -1.14(0.04) | -0.84(0.04) |
| Difference vs. pioglitazone 35 + Met | -0.30(0.05) | |
| 95% two-sided CI | [-0.40,-0.20] | |

Subgroup analysis:

The treatment-by-ethnicity interaction was significant (p=0.1). The Hispanic/Latino patients receiving muraglitazar had greater reductions in $HbA_{1c}$ than the non Hispanic/Latino patients (Fig 26).

*Figure 26 Mean $HbA_{1c}$ change from baseline by ethnicity – Active control Metformin add on*




**2.3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

The geographical regions were not considered in the analysis model but the ethnicity was. The treatment-by-ethnicity interaction was not consistently significant across studies and across doses (2.5 and 5 mg). The treatment-by-gender interaction is consistent across the 4 placebo- or low-dose controlled studies. The delta for 5 mg minus placebo was usually 0.5% larger for females than males for each study. Individual study treatment-by-gender interaction p-values were 0.06, 0.04, 0.007, and 0.016 for the muraglitazar 5 mg group and the control group. Figure 27 shows that female had greater $HbA_{1c}$ reduction than male. Figure 28 shows greater $HbA_{1c}$ reduction in Hispanic/Latino than non Hispanic/Latino in some of the studies. Treatment-by-age group was not significant (Fig 29).

*Figure 27 Mean $HbA_{1c}$ change from baseline by protocol and gender*

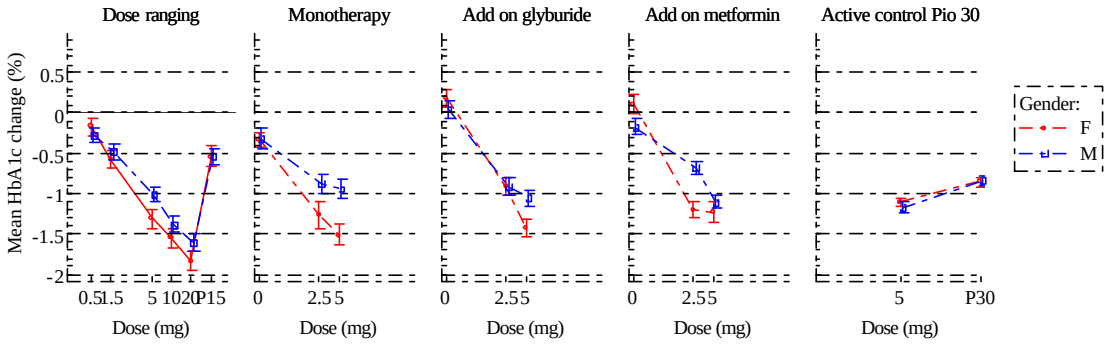



*Figure 28 Mean $HbA_{1c}$ change from baseline by protocol and ethnicity*

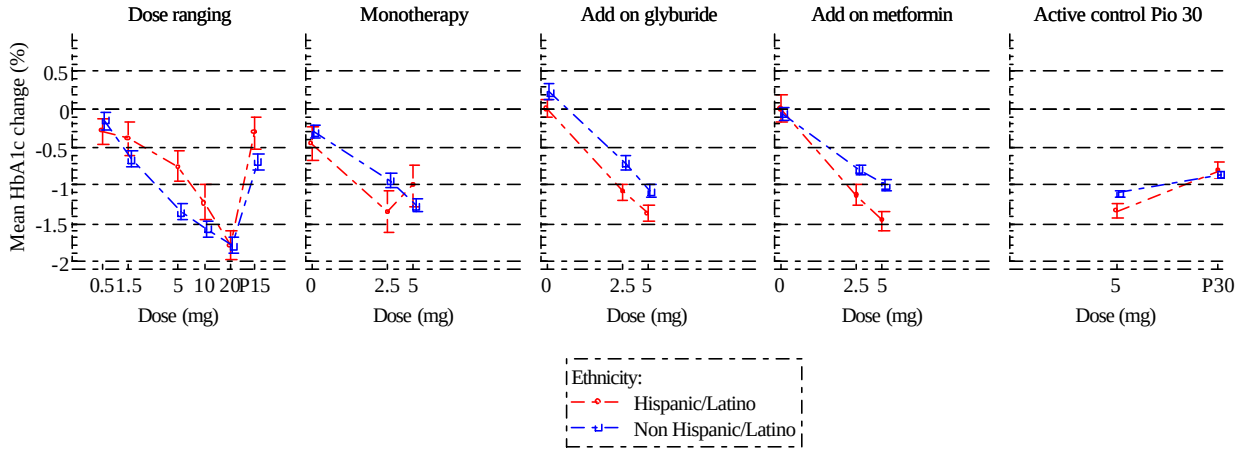
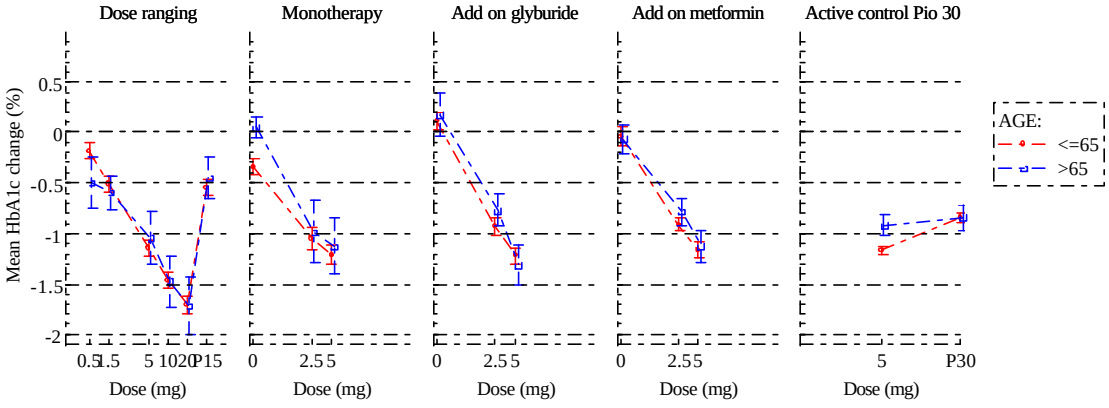



*Figure 29 Mean $HbA_{1c}$ change from baseline by protocol and age group*




At week 12 the difference in mean percent triglycerides change from baseline between 2.5mg or 5 mg muraglitazar-treated patients and control were statistically significant (Table 30, Fig 30). Figure 31 displays the medium triglycerides change from baseline over time.

*Table 30 Sponsor's analysis in TG percent change from baseline*

| Study | Dose (mg) | n | Baseline | Week 24 | Mean % Change (SE) | Mean difference from control [C.I.]* |
|---|---|---|---|---|---|---|
| Dose ranging | Mur 0.5 | 230 | 201.04 (155.65) | 190.40 (159.46) | -3.74% (2.32) | |
| | Mur 1.5 | 251 | 188.73 (136.17) | 175.47 (115.89) | -6.47% (2.16) | -2.84% [-9.00, 3.74] |
| | Mur 5 | 234 | 186.30 (116.00) | 140.41 (70.35) | -21.10% (1.89) | -18.03% [-23.31, -12.38] |
| | Mur 10 | 244 | 194.52 (240.96) | 122.60 (72.02) | -31.71% (1.60) | -29.06% [-33.59, -24.22] |
| | Mur 20 | 236 | 176.22 (107.27) | 102.64 (52.80) | -40.96% (1.41) | -38.67% [-42.61, -34.45] |
| Monotherapy | Mur 2.5 | 111 | 192.83 (93.98) | 158.09 (76.99) | -17.93% (2.52) | -16.50% [-23.29, -9.10] |
| | Mur 5 | 112 | 194.07 (99.38) | 141.16 (74.44) | -27.44% (2.22) | -26.17% [-32.16, -19.64] |
| | Placebo | 114 | 186.85 (110.45) | 186.43 (120.52) | -1.72% (2.98) | |
| Add on glyburide | Mur 2.5+Gly | 183 | 196.67 (116.38) | 169.21 (94.43) | -13.87% (2.01) | -16.53[-21.68, -11.05] |
| | Mur 5+Gly | 192 | 203.62 (110.23) | 147.56 (74.84) | -26.12% (1.68) | -28.40[-32.76, -23.75] |
| | Placebo+Gly | 197 | 192.95 (110.62) | 202.78 (140.14) | 3.18% (2.32) | |
| Add on metformin | Mur 2.5+Met | 228 | 197.79 (116.07) | 167.23 (83.85) | -13.88% (1.82) | -16.57% [-21.41, -11.42] |
| | Mur 5+Met | 201 | 208.02 (121.48) | 141.32 (68.38) | -29.20% (1.60) | -31.42% [-35.53, -27.04] |
| | Plb+Met | 212 | 197.01 (177.78) | 207.09 (151.23) | 3.22% (2.26) | |
| Active control | Mur 5+Met | 571 | 205.50 (125.09) | 142.35 (75.33) | -28.43% (0.89) | -16.36% [-19.22, -13.39] |
| | Pio 30+Met | 555 | 202.75 (128.44) | 173.29 (108.27) | -14.44% (1.08) | |

*2-sided, 95%

*Figure 30 Triglyceride mean percent change from baseline difference of muraglitazar to control by treatment group and study*

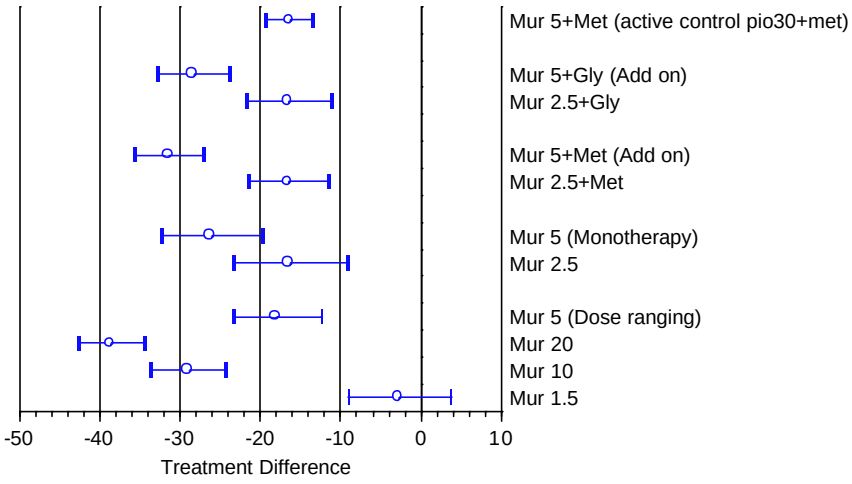
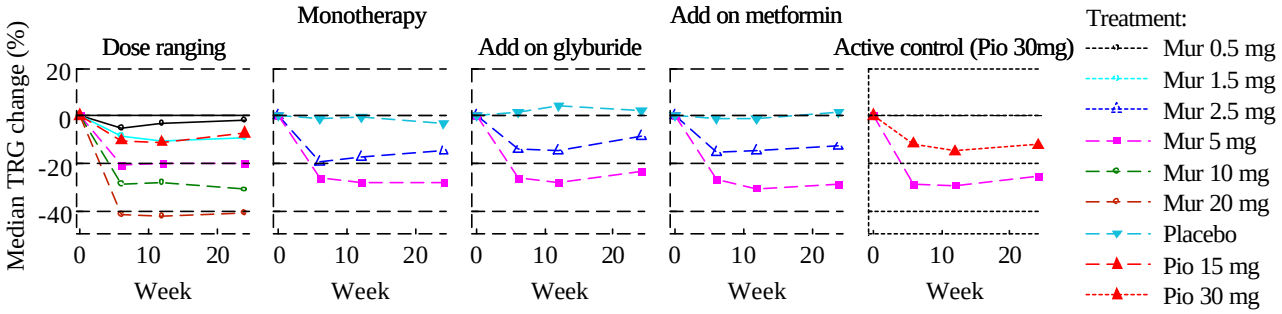


*Figure 31 Median triglyceride changes from baseline over time*




## Safety Endpoints

Weight gain

Patients treated with muraglitazar had a dose related increase in weight. The means were 1.8 to 2.2 kg for the 2.5 mg dose and 2.9 to 3.6 kg for the 5 mg dose (Table 31). Figures 32-34 show that muraglitazar as add-on therapy to glyburide had the greatest increase of weight.

*Table 31 Sponsor's analysis in weight change (kg) from baseline*

| Study | Dose (mg) | n | Baseline | Week 24 | Change (SD) | Mur minus control (SE) [C.I.]* |
|---|---|---|---|---|---|---|
| CV168 006 | Mur 0.5 | 231 | 88.35 (17.01) | 87.22 (16.85) | -1.13 (3.41) | |
| | Mur 1.5 | 253 | 88.87 (17.27) | 88.65 (17.57) | -0.22 (3.09) | 0.91 (0.35) [0.22,1.60] |
| | Mur 5 | 235 | 88.87 (16.93) | 90.48 (18.04) | 1.60 (3.66) | 2.73 (0.36) [2.03,3.43] |
| | Mur 10 | 245 | 88.95 (18.04) | 92.14 (18.65) | 3.19 (4.24) | 4.32 (0.35) [3.63,5.01] |
| | Mur 20 | 236 | 90.97 (16.87) | 95.84 (17.91) | 4.87 (4.63) | 5.98 (0.36) [5.28,6.68] |
| CV168 018 | Mur 2.5 | 111 | 90.51 (18.94) | 91.56 (19.24) | 1.05 (3.61) | 1.83 (0.47) [0.92,2.75] |
| | Mur 5 | 112 | 88.67 (20.43) | 90.77 (21.16) | 2.10 (3.65) | 2.88 (0.47) [1.97,3.80] |
| | Placebo | 114 | 88.22 (21.60) | 87.44 (21.46) | -0.78 (3.20) | |
| CV168 021 | Mur 2.5+Gly | 183 | 83.09 (18.70) | 85.72 (18.74) | 2.62 (2.94) | 2.20 (0.33) [1.55,2.85] |
| | Mur 5+Gly | 191 | 82.64 (16.43) | 86.70 (16.95) | 4.06 (3.50) | 3.63 (0.33) [2.99,4.28] |
| | Placebo+Gly | 197 | 87.21 (20.00) | 87.65 (20.52) | 0.44 (3.16) | |
| CV168 022 | Mur 2.5+Met | 229 | 89.92 (18.95) | 91.34 (19.83) | 1.41 (3.16) | 2.12 (0.29) [1.54,2.70] |
| | Mur 5+Met | 202 | 88.77 (19.22) | 91.52 (20.04) | 2.75 (3.39) | 3.48 (0.30) [2.89,4.08] |
| | Placebo+Met | 212 | 88.64 (17.47) | 87.90 (17.74) | -0.74 (2.78) | |
| CV168 025 | Mur 5+Met | 576 | 90.32 (17.14) | 91.71 (17.73) | 1.39 (3.71) | 0.84 (0.20) [0.44,1.24] |
| | Pio 30+Met | 567 | 90.97 (17.07) | 91.53 (17.62) | 0.56 (3.19) | |

- 2-sided, 95%

*Figure 32 Difference from control in weight change from baseline*

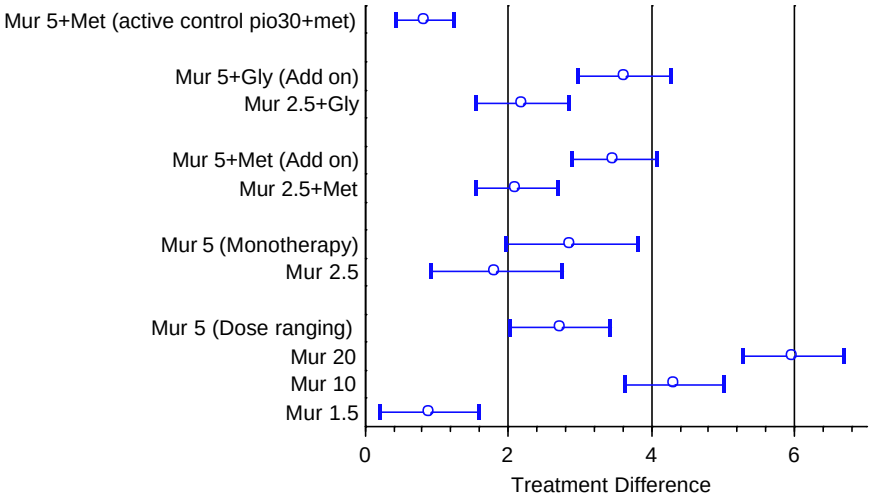



*Figure 33 Mean weight gain by treatment dose*

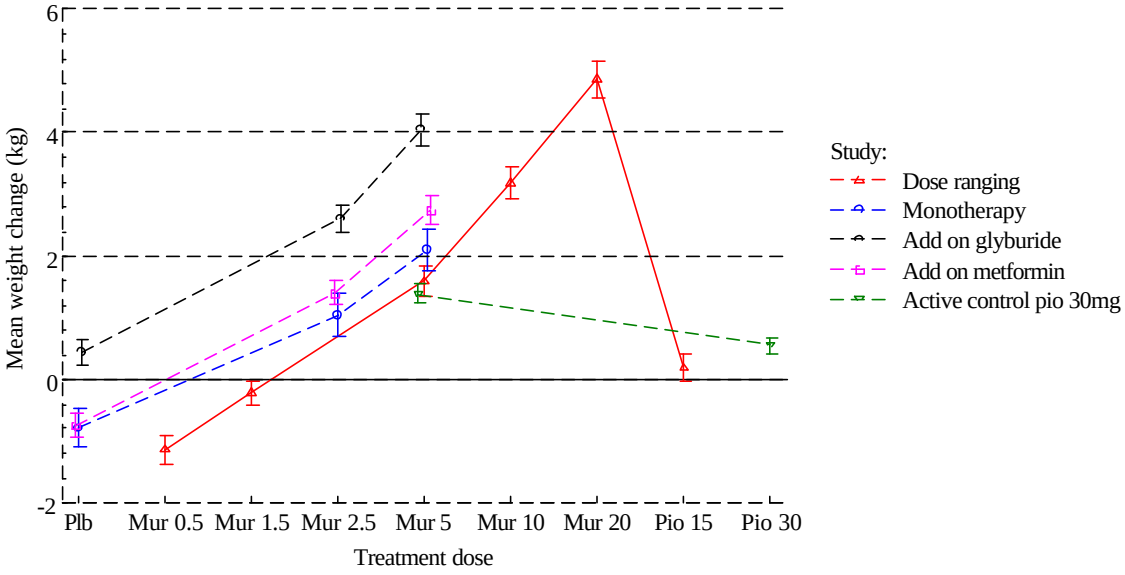
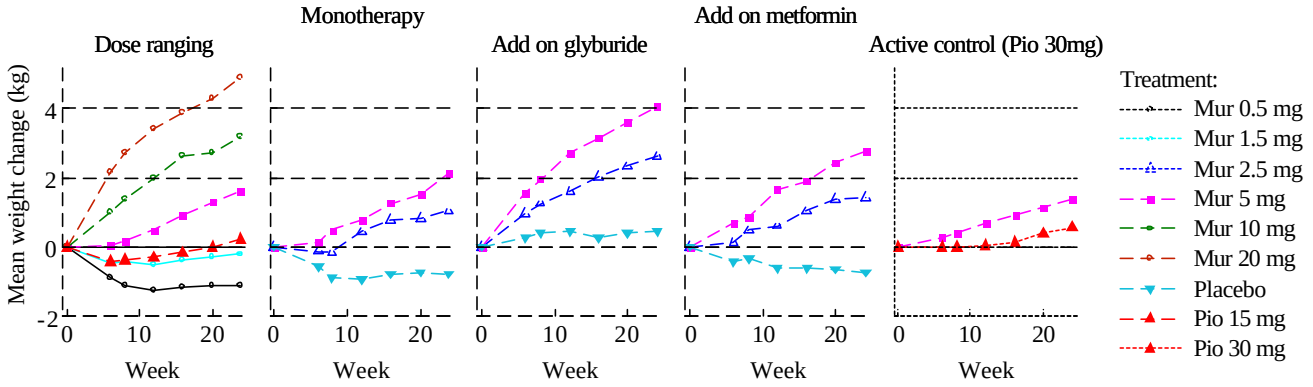


*Figure 34 Mean weight gain over time*




## 2.4 CONCLUSIONS AND RECOMMENDATIONS

Muraglitazar 2.5 mg and 5.0 mg were efficacious in $HbA_{1c}$ change from baseline in monotherapy and add on therapies of metformin and glyburide. The lowest dose for 1.5 mg studied was also efficacious. The $HbA_{1c}$ lowering at 2.5 mg was -0.9% to -1.0% and 5 mg was -1.1% to -1.2% doses across all studies. Baseline $HbA_{1c}$ was approximately 8.0% for the randomized treatment groups in all studies. The small increment in efficacy in $HbA_{1c}$ for the 5 mg over 2.5 mg needs to be balanced with the risk in deciding the labeled doses for muraglitazar.

## 2.5 APPENDIX

2.5.1 GRAPHS

*Figure 35 Mean $HbA_{1c}$ change from baseline (%) by study dose -*

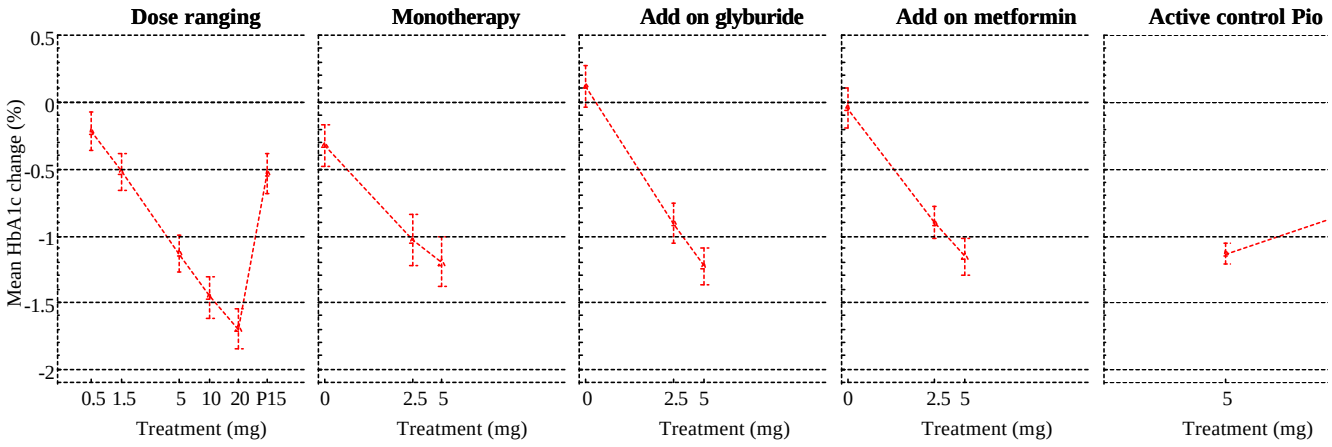


*Figure 36 Mean $HbA_{1c}$ change from baseline by the ethnicity of Hispanic/Latino*

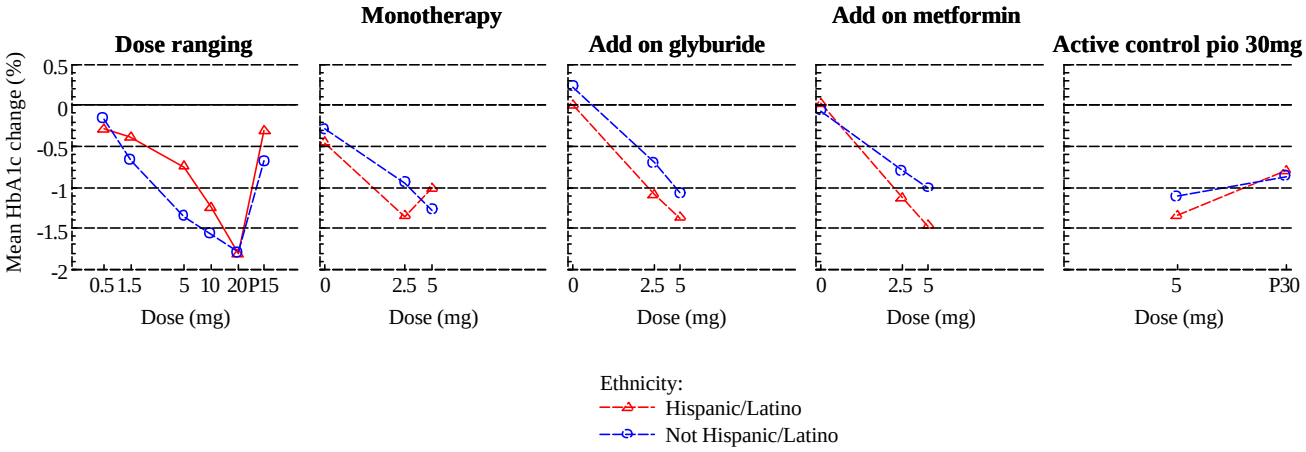



*Figure 37 Mean $HbA_{1c}$ change from baseline by gender*

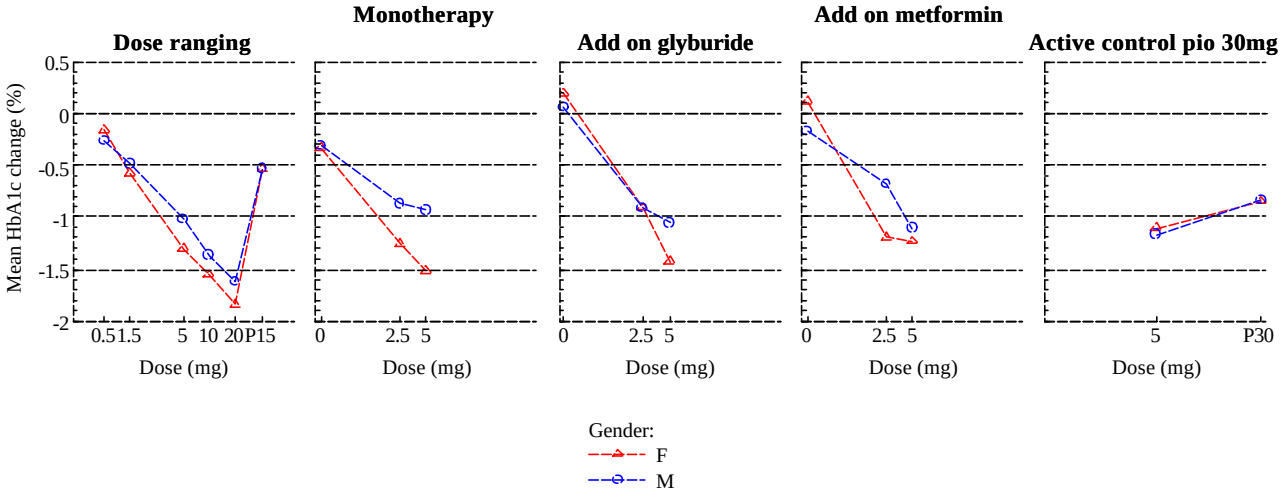


*Figure 38 Mean $HbA_{1c}$ change from baseline by Age*

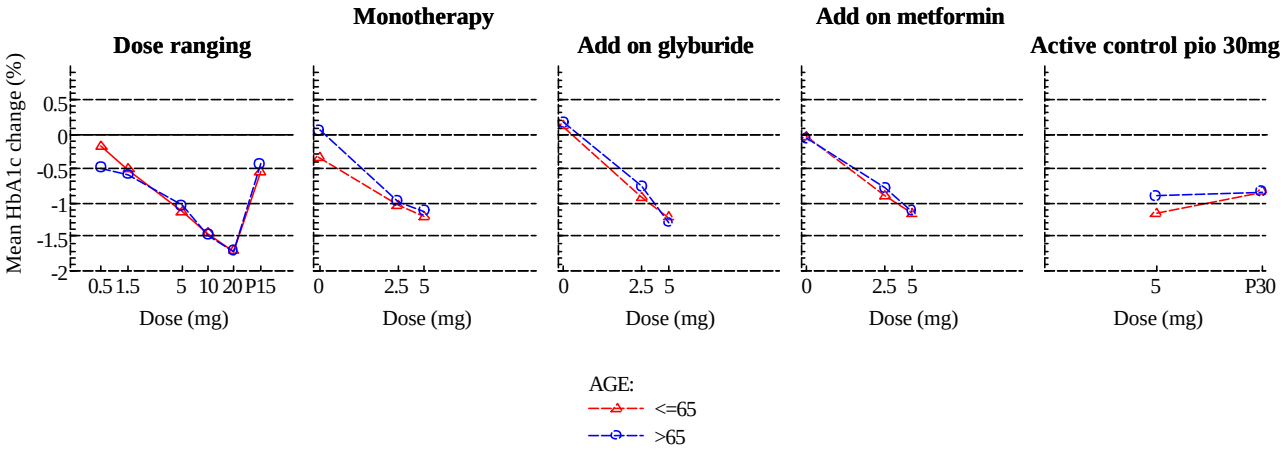



*Figure 39 $HbA_{1c}$ change from baseline by baseline*

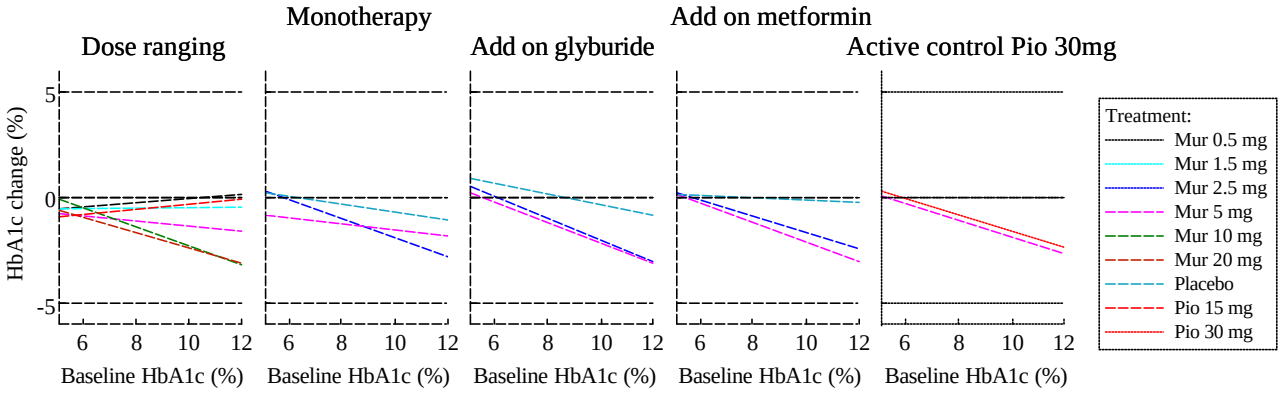


*Figure 40 Mean $HbA_{1c}$ change from baseline by baseline diuretic use*

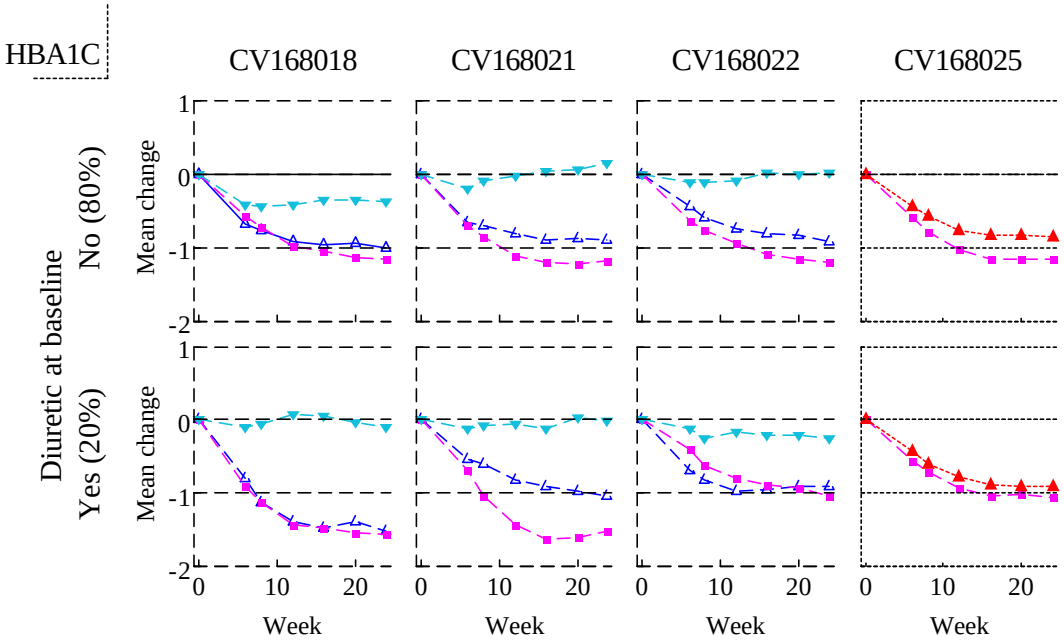



*Figure 41 Mean BMI change ($kg/m^2$) by treatment dose*

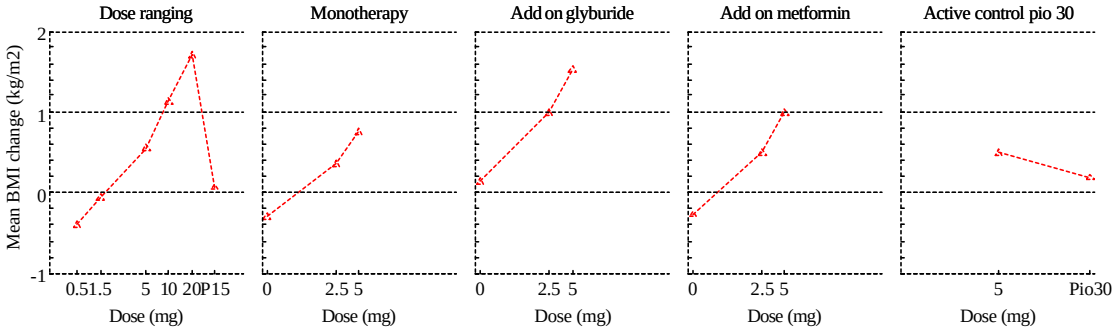



*Figure 42 Mean BP change ($kg/m^2$) by treatment dose*